160-145-A Reed AN=390
11-15
1030

PRELIMINARY SURVEY OF CHEMICAL COMPOSITION, CONTAMINATION, AND ASSOCIATED HEALTH HAZARD OF PLASTIC PIPE FOR POTABLE WATER SUPPLY

NOVEMBER 14, 1980

THOMAS REID ASSOCIATES
PALO ALTO, CALIFORNIA

PRELIMINARY SURVEY OF CHEMICAL COMPOSITION, CONTAMINATION AND ASSOCIATED HEALTH HAZARD OF PLASTIC PIPE FOR POTABLE WATER SUPPLY

NOVEMBER 14, 1980

THOMAS REID ASSOCIATES

Palo Alto, California

Thomas S. Reid
Karen G. Weissman, Ph.D.
Barbara Castro
Carol Manahan
Tay Peterson

READER'S GUIDE

This study is a preliminary survey of the chemical constituents of plastic pipe, potable water contamination, and the associated health hazard. The study was prepared by Thomas Reid Associates (Palo Alto) under contract to Thomas R. Adams, Adams, Broadwell and Russel attorneys representing Local 467 Plumbers and Steamfitters Union, AFL-CIO. The material is an informational submission to the California Housing and Community Development Commission. The study specifically addresses proposed amendments to the Uniform Plumbing Code (Section 401 (e)).

Five kinds of plastic pipe are being considered for domestic potable water use in residential construction: polyvinyl chloride (PVC), chlorinated polyvinyl chloride (CPVC), acrylonitrile-butadiene-styrene (ABS), polyethylene (PE), and polybutylene (PB). Contamination of the water supply by plastic pipe constitutes a health hazard. The purpose of this study is to indicate the scope of the problem which must be considered in order to fully evaluate the degree of the health hazard. In this study we consider the population at large -- the families that will be using water from installed plastic piping systems. We do not consider the hazards of occupational exposure for people installing the plastic piping systems.

Chapter I introduces the philosophy of the study, describes the methods used, and the limitations of the results presented here. The reader is invited to pay particular attention to the limitations. Assessing the hazard of plastic pipe is a complex task and this report is intended only to give an indication of the extent of the problem.

Chapter II describes the range of chemical substances which can be present in pipe applied to domestic water service. This is the starting point of the study: if a substance is present in the pipe, then it <u>may</u> be a contaminant.

Chapter III assesses the likelihood that chemical constituents will actually contaminate the water supply and be communicated to the population at risk. This includes a discussion of the water analyses conducted by Montgomery Laboratories for the Department of Health Services, Hazard Evaluation System (HES).

Chapter IV summarizes information available on the health effects of some of the compounds. This gives an indication of what the impact might be on the population at risk.

TABLE OF CONTENTS

LIST OF TABLES

SUMMARY

This report examines the chemicals found in those plastic pipes under consideration by the California Commission on Housing and Community Development for use for potable water supply. Generically, the five types of pipe are acrylonitrile-butadiene-styrene (ABS), polyvinyl chloride (PVC), chlorinated polyvinyl chloride (CPVC), polyethylene (PE), and polybutylene (PB). We consider which chemicals found in the pipe can enter the water supply and the health risks posed by these. Only with a complete understanding of this can a reasonable decision to license these materials be made. At this time, the necessary understanding is seriously deficient and there is no proof that plastic pipe for water supply does not pose an unacceptable public health hazard.

The major findings of our study are as follows:

(1) There is a wide variety of chemical substances present in the five types of plastic pipe. In addition to the polymers ("plastic") making up the bulk of the pipe, there are compounds used in the manufacture of the pipe such as solvents, monomers, plasticizers and stabilizers, as well as impurities and reaction products between other chemicals. Earlier data and a November 1980 analysis of some of the pipe in question by California Analytical Laboratories, Sacramento, show that the impurities include known carcinogens such as chloroform, benzene, acrylonitrile, and styrene, as well as other compounds on the EPA list of priority pollutants.

(2) The James M. Montgomery labs report is the only study we know of to date which addresses the question of which substances present in plastic pipe can enter the water supply. Our review of this report supports our conclusion that this single study is not a sufficient basis for a decision to license the five kinds of pipe under consideration. Our conclusion is based on the following definite limitations of this report:

(a) The Montgomery study only examined a previously agreed on list of compounds, selected because they were priority pollutants or known solvents. It was not an attempt to analyze all actual contaminants from plastic pipe in the water. It is dangerous to assume that Montgomery had done an exhaustive analysis of all possible pollutants, when this was not the case.

(b) The Montgomery study only examined two kinds of pipe, PVC and CPVC, each made by a single manufacturer. The results cannot be extrapolated to ABS, PE or PB pipe, or even PVC and CPVC pipe made by other manufacturers. A review of plastics literature and a search of U.S. patents revealed that the manufacturing processes of different pipe fabricators can be quite different, and that the same manufacturer can change its process from time to time. A different process or a different kind of pipe means that different amounts and different types of chemicals have the potential to contaminate the drinking water supply. Obviously, the Montgomery study only shows the potential risk from the pipes it examined.

(c) The Montgomery results themselves do not allow reliable statistical inference that there is any method of pre-treating the pipe before use (ie. flushing) which will reduce the public health hazard from chemical contaminants. Although flushing is an intuitively attractive idea, there is no data to prove it effective or to show how long flushing is required.

(d) Among the problems encountered in the Montgomery tests were the problem of resolving too many compounds, high levels of solvent interference with compounds of interest, presumably a large residual set of unanalyzed material, and too few replicates of individual tests.

The Montgomery study is an adequate first attempt at a very difficult technical problem, but its results are preliminary in the extreme. Only a large-scale study of water contamination from all types of pipe would support the decision at hand. If any conclusion is to be drawn from the Montgomery data, it must be conservative; that is, the data presented show at least some high values for each contaminant in the water and these should be considered in interpreting the health hazard of the system.

(3) The population at risk exposed to the substances in the pipes will be all of the occupants of new homes outfitted with this material. This population will ultimately comprise millions of persons of all ages and both sexes. Among the population at risk will be individuals with high sensitivity to toxic, carcinogenic, mutagenic, and teratogenic substances, such as young children or pregnant women. They will be exposed to these compounds through drinking water, cooking water, bathing and even laundry. While the government tries to protect the health of these sensitive individuals, as with careful control of drugs, the dose of chemicals they would receive from the plastic pipe would be uncontrolled and unregulated.

(4) In addition to a human health risk there is a definite risk to the environment from the waste discharge of water flowing through plastic pipes. The subject chemicals will add to the existing load of pollutants known to have serious environmental effects because they display all of the characteristics of such chemicals. Namely, they are toxic or carcinogenic, are selectively partitioned into and accumulated in living organisms and food chains, are persistent (long half-lives) and may be widely dispersed in the environment.

The conservative levels of carcinogens and other toxins found in the Montgomery study are tens to hundreds of times greater than the EPA "acceptable risk levels" (1 cancer in 1 million persons exposed). At best, the licensing of plastic pipe for potable water will expose a large population to long term, low-level, chronic toxicity of unknown danger. At present, the data concerning chemicals in the pipe, the levels entering the water supply over time, time population health effects, and the environmental effects are incomplete and inconclusive. What evidence there is indicates that the chemicals present a potentially serious risk. In the absence of conclusive information to the contrary, a blanket decision to license PVC, CPVC, ABS, polyethylene and polybutylene pipe for domestic water supply cannot reasonably be supported.

CHAPTER I -- INTRODUCTION

A. APPROACH

This report assesses the degree of public health hazard associated with the use of plastic pipe for domestic water supply. As this study shows, that assessment is difficult because it requires detailed understanding of the long term health effects of nearly constant exposure to low levels of a host of chemical substances. We approach the general question through a chain of three logical steps.

Since we are dealing with complex chemical substances, we first need to know what types of chemicals are involved. The simplest way to learn this is to find out what chemical substances are present in the pipes proposed for use in California. By itself, this does not show the range of chemical substances to which the population will be exposed, but it does establish a starting point for the investigation. The reasoning is simple. If a chemical substance is not present in the pipe, then it is not a possible contaminant of the water supply. On the other hand, if a chemical substance is present in the pipe, then it must receive serious consideration until it can be proven conclusively that it does not enter the water supply and therefore, cannot be communicated to the population at risk.

The second step is to determine which of the chemical substances present in the pipe can enter the water supply. In this study we focus on water supply as the medium of exposure since we do not examine the occupational hazards associated with installation or handling of plastic pipe. The importance of this second step is clear: if a substance cannot enter the water supply, then it will pose no hazard, regardless of how toxic it may be in its isolated form. On the other hand, if the substance is shown to enter the water supply then it must be proven to cause no health effects.

The third step is to evaluate the nature of the health hazard posed by the substances which can be communicated through the water to the population at risk. This involves both laboratory studies of the effects of the chemical substances, and simultaneous consideration of the concentration over time of the water supply contaminants introduced from the plastic pipe.

Ideally, an evaluation of plastic pipe hazard could be made by simply following the three logical steps in order. Unfortunately, as it will be seen in this report, it is difficult to get complete information needed to evaluate each step independently. There is uncertainty as to the exact chemical constituents of the pipe itself; this is aggravated by the need to consider impurities, degradation products, and ongoing changes in manufacturing processes. The second step is even harder, since theoretical considerations of solubility and migration through the polymer matrix make poor predictions at low concentrations. Laboratory analysis of the water is difficult -- since some substances are undoubtedly present for which analytical procedures have not been established and a comprehensive testing program would necessarily cover a diverse range of pipes and manufacturers. Most difficult of all is the third step, because of the large number of chemicals involved and the difficult question of chronic toxicity to a population which may contain highly susceptible members such as pregnant women or young children.

B. METHODOLOGY USED IN THIS STUDY

This study identifies the fundamental issues underlying the hazard evaluation problem. We show the scope of the problem and indicate the uncertainties surrounding the answers now available. The purpose is to indicate where a decision maker may feel an appropriate need for caution. To this end we have used several specific tools.

Information on the chemical constituents of pipe is drawn from consideration of basic polymer technology. Using published sources we get an indication of the range of substances that may be present in the pipe. Apart from the polymer itself, this source is most useful for information about the additives used to improve the pipe's properties. Information on impurities and degradation products is more difficult to obtain. We have supplemented the polymer literature with laboratory testing of pipe material itself. We have also reviewed recent patents for chemical substances registered with the U. S. Patent Office to to show how the range of chemical substances may change in the future due to the adoption of improved methods.

The primary source of information for this proceeding on the possible level of contaminants in the water is the study done by Montgomery Engineers for the Pipe Manufacturers and the California Department of Health Services, Hazard Evaluation System (HES). We explain why this source has severe limitations to support decision-making on plasic pipe use. We also include some consideration of the physical and chemical processes whereby material in the pipe can be leached into the water supply.

The health hazard of many of the chemical substances of interest are addressed broadly in the scientific literature. Much information is summarized in the series of reports culminating in the October 17, 1980 Hazard Evaluation System Publication. To support our analysis of health effects we have used the HES publication and an independent review of current toxicology and environmental impact literature for some of the chemicals.

C. LIMITATIONS

This report has several significant limitations which should be borne in mind when drawing conclusions from the information presented here. Since the subject of the study is health hazard, incomplete information may lead to an underestimate of the actual degree of hazard involved. The principal constraint to the study is the time available for preparation. While we identify many uncertainties, a more comprehensive program could resolve many of these. In particular, a program where ongoing laboratory study and literature research were coordinated to further refine results could be effective in resolving with the wide range of compounds and phenomena involved.

One major, specific limitation for the study is reliance on published information. No attempt was made to access proprietary manufacturing information about the composition of pipe proposed for use in California. The term "plastic pipe" embraces a host of different materials. In our reliance on general published descriptions, we have undoubtedly missed some specific combinations of additives which could have significant health implications. Conversely, we may have inadvertantly included some chemical substances which

may be not be used by manufacturers seeking a California market. Only a mandatory disclosure program for all prospective vendors could overcome this limitation.

A second limitation which affects our information on the content of the pipe is the lack of time needed to perfect laboratory methods for quantitative analysis of the plastic pipe itself. Many workers have addressed the problem of quantifying the presence of known additives. Quantitive extraction and identification of all compounds present in the pipe poses a more difficult problem. We could not obtain a sample of polybutylene pipe in time for analysis.

In discussing the concentration of contaminants in the water supply, we are forced to rely on the Montgomery Engineers Report to HES. This is an important limitation for two reasons. First, there are analytical difficulties which may make some of the results less reliable than others. Second, the test examined only polyvinyl chloride (PVC) and chlorinated polyvinyl chloride (CPVC) pipe and not acrylonitrile-butadiene-styrene (ABS), polyethylene (PE), or polybutylene (PB) pipe. These latter are also under consideration by the Commission.

The literture search was limited to results published primarily in the last three years (1977-80). While this places a proper emphasis on the current state of knowledge, it still exempts a large body of potentially relevant research from our review. We also limit the literature search to several selected chemicals. Generally, we have emphasized those compounds of uncertain status but definite risk, for this typifies the problem before the commission: needing to evaluate the health effects of compounds that have not yet been subject to formal study and rule making by federal agencies. We have included, but with less detail, those compounds which are formally recognized government listed carcinogens and priority pollutants.

CHAPTER II -- THE CHEMICAL CONSTITUENTS OF PLASTIC PIPE

The purpose of this chapter is to identify a range of chemical substances which may potentially contaminate water. To do this, we introduce the five types of plastic pipe material proposed for use in California and show the need for additives to improve their physical properties. We also address the problem of contamination and degradation products which form when the plastic ages.

The plastic of plastic pipe is itself a chemical compound. Plastic is the general term given to substances known as polymers. Polymers are large molecules made up of many repeating subunits which are called monomers. In the case of polyvinyl chloride (PVC) and polybutylene (PB), the monomer units are all the same for one type of plastic. Poly means "many" and the monomer in those examples are vinyl chloride or butylene respectively. In the case of acrylonitrile-butadiene-styrene (ABS), three different monomers are involved. Typically, some 500 to 1000 of the small monomer molecules are joined together to form the large polymer molecules. It is the properties of the polymer that give the plastic its useful characteristics.

When we speak of manufacturing we refer to all of the stages involved, from prepation of the polymer, through formulation with additives to improve its chemical or physical properties, to actual fabrication into pipe. Installation refers to the steps needed to turn the pipe material into a domestic water system. Here we are primarily interested in solvent welding, which is the most common means of joining pipe components together.

Some of the chemicals of concern here are listed in Appendix A. They include the monomers and the commercially used additives for the five types of plastic. We have little published information on impurities at present.

A. BASIC TYPES OF PLASTIC USED FOR PIPE

Five types of plastic pipe are proposed for use in California. They are the major types of plastic used in industrial installations for non-potable water and for drain-waste-vent systems in domestic plumbing. Each type of plastic has fundamental properties, such as cost, service temperature, and stability which make it suitable for various applications.

1. Polyvinyl chloride (PVC)

Polyvinyl chloride is one of the three most commonly used plastics. It first became widely commercialized in 1936. Much of PVC's appeal is its low cost, since vinyl chloride monomer is easily synthesized from a wide variety of feedstocks. PVC's chemical and physical properties are also easily varied by the addition of chemicals to the bulk polymer.

PVC is most commonly prepared by polymerization of vinyl chloride gas under pressure in a water suspension. Other chemicals are added to the reaction mixture to initiate polymerization and to control the process. The mixture is reacted until 90% of the vinyl chloride is consumed, and the slurry of small polymer particles is separated, washed and dried.

In this portion of the manufacturing process, there are several sources of impurities. Vinyl chloride is manufactured from hydrocarbon feed stocks by chlorination. In the ethylene process, one of the intermediaries is ethylene dichloride. This substance and other low molecular weight chlorinated hydrocarbons are likely to be retained as low level impurities in the vinyl chloride monomer used for polymerization. Despite the washing of the polymer slurry, it is probable that some of the materials used in the reactant mixture are incorporated in the solid plastic granules, particularly if they have mutual solubility. Trichloroethylene (trichloroethene) is a commonly used transfer agent in suspension polymerization. Vinyl chloride itself is present in excess. Some quantities of these materials may be retained in the finished plastic.

Raw, uncompounded polyvinyl chloride has relatively poor heat and light stability compared with other, more expensive polymers. It is a colorless, rigid material, naturally flame-retarding due to the high chlorine content. At temperatures above 160°F or in sunlight, pure PVC begins to break down. Chemically, there are two principal degradation processes: dechlorination and oxidation. With the former, chlorine is lost from the polymer, forming hydrogen chloride and leaving a double bond in the polymer chain, which encourages subsequent degradation. In the latter, oxygen from the air abstracts hydrogen. Both processes result in weaker polymer chains, and ultimately a variety of chain fragments, including lower molecular weight chlorinated hydrocarbons and free initiator molecules.

Commercial success of PVC depends on the extensive use of stabilizers to alleviate the effects of degradation. The more important stabilizers include lead compounds, such as basic lead carbonate and di-basic lead phthalate; metal soaps such as barium, cadmium, and zinc laurates, octoates and stearates; cadmium and barium phenates; organo-tin compounds, such as di-butyl tin di-laurate and maleate; and epoxidized oils, such as epoxidized linseed and soybean oils. The exact mode of activity of the stabilizers is little understood. It appears that they act partially in reaction with the polymer chain and partially to scavenge oxygen entering the plastic matrix. Both modes of action result in gradual degradation of the stabilizer molecules, with subsequent release of lower molecular weight heavy metal compounds. This would be expected to increase with the age of the plastic.

Plasticizers such as di(ethyl-hexyl) phthalate (DEHP) are a most important class of additives for PVC. Generally, they are low molecular weight compounds which are mutually soluble with PVC; and, when mixed in with the polymer, give it flexibility or rubber-like qualities. Flexible, plasticized PVC usually contains 20-40% plasticizer by weight.

"Rigid" PVC is a somewhat less highly polymerized plastic intended for applications where the application does not require the flexibility conferred by large quantities of plasticizer. Plastic pipe is considered a rigid application and need not be highly plasticized as are the more flexible forms of PVC used in cable installation, upholstery, and packaging.

Unfortunately, pure PVC is a difficult material to extrude into complex or continuous shapes. Because of its sensitivity to heat, it is important that the raw PVC not be kept at elevated temperatures in the forming process. However, if the extrusion temperatures are too low, the material is not soft enough to be formed easily into the proper shape. Rigid applications require

extensive use of stabilizers to protect the material during manufacture, even where the end use does not entail exposure to higher temperatures. Additionally, some plasticizing materials are commonly used to aid in extrusion. Modern machinery, such as the in-line screw pre-plasticizing injection molding machines can make use of unplasticized raw PVC material. In these systems, a chemical additive, although a plasticizer, serves more as a temporary softening agent or lubricant to aid in manufacture. The material, of course, remains with the finished product, but is present at lower levels than in most highly plasticized PVC products.

The requirements for a plasticizer are met by a broad range of chemical substances, some of which serve additional functions as stabilizers. Some of the more important plasticizers include the aryl phosphates (tri-tolyl phosphate) and the alkyl phthalates (diethyl-hexyl phthalate).

PVC is most commonly bonded by welding, using either heat or solvents to soften the polymer. PVC has limited solubility -- the most common solvents are oxygen containing solvents such as tetrahydrofuran, cyclohexanone, and ketones, or chlorinated solvents such as trichloroethylene. Most common cements for joining PVC pipe rely on the solubility of the plastic to effect the weld. Occasionally small quantities of lower molecular weight PVC are dissolved in the solvents first to give the cement suitable thickness for handling during use.

2. Chlorinated polyvinylchloride (CPVC)

The softening point of PVC is around 170°F. This can be raised to temperatures above the boiling point of water if the chlorine content of the plastic is increased. A useful pipe material is produced by chlorinating polyvinyl chloride after the polymerization stage. Because chlorination raises the maximum service temperature from about 150°F to about 210°F, CPVC ismost commonly applied in higher temperature applications where more durable polymers are considered too expensive. For this reason, CPVC would be required in a domestic plumbing system carrying hot water.

Depending on the extent of reaction, the chlorine content can be increased to roughly two-thirds by weight, and the polymer is chemically similar to a polymer resulting from a mixture of vinlyl chloride and s-dichloroethylene. The overall low cost of vinyl chloride monomer makes it cost effective to use the post-polymerization chlorination to produce CPVC rather than to produce a similar plastic from different raw materials. Most commercial CPVC is produced by low temperature chlorination. PVC granules are treated with a swelling agent, such as chloroform, to allow more intimate contact with the chlorinating agents. They are then dispersed in water and treated with chlorine gas.

The sources of impurities for CPVC include those for PVC itself. In addition there is contamination by the swelling agent and by the results of rather broad spectrum chlorination on any smaller molecular fragments present in the polymer matrix.

It is difficult to extrude CPVC because the higher chlorine content decreases stability and increases the viscosity or thickness of the compound at molding temperatures. For this reason, CPVC manufacture may incorporate more plasticizers. The types and amounts of plasticizers will vary from

manufacturer to manufacturer, and from batch to batch depending on operating conditions prevailing at the time the pipe is made.

Although CPVC is more resistant to softening, it is subject to the same thermal degradation and oxidation as PVC, and has the same requirement for stabilizers, anti-oxidants and ultra-violet absorbants. CPVC welding can be done with solvents similar to those used for PVC.

3. Acrylonitrile-butadiene-styrene (ABS)

ABS is a polymer of three different basic units, as its name implies. Each of the monomers is used in formulating other types of plastics. In ABS, the combination provides rigidity, toughness, moldability at relatively low cost compared with other plastics. ABS first became widely commercialized in 1948.

There are several commercial methods of preparing ABS. Generally some or all of the ingredients are partially polymerized in order to control the structure of the final ABS polymer. The composition varies, but typically styrene contributes somewhat less than half of the weight with acrylonitrile ranging from one-quarter to one-third, and butadiene making up the balance.

The manufacture of the individual monomers introduces an assortment of potential impurities in the polymer. For example, styrene is usually made from ethyl benzene and is slightly contaminated with some of its intermediates. Other impurities result from the incorporation of surfactants, solvents, or transfer agents, such as mixed tertiary mercaptans used in the polymerization process. The finished polymer may also contain unreacted monomer and short low molecular weight polymer fragments.

ABS does not show the same sensitivity to heat as PVC, yet it is degraded by sunlight and generally held to have poor weathering properties. In commercial applicaions, stabilizers may be added to improve durability.

Because of its greater heat resistance and lower viscosity at higher temperatures, ABS is easily molded or extruded into joints and pipes. The basic properties of the product are conferred by the polymer itself, and extensive plasticizing is not needed. Some manufacturers may select stabilizers which improve weathering and also act as lubricants in the molding process.

Since ABS is attacked by many solvents, solvent welding is easily applied to ABS pipe. In addition to the oxygen or chlorine containing solvents used for PVC, ABS cements can include cheaper components, such as aromatic and aliphatic hydrocarbons: toluene, xylene, hexane, etc. In addition to solvents, cements will contain dissolved polymer for proper viscosity and to fill the voids between mating parts. Because of ABS compatibility with its components, cements could use simple styrene plastic as the filler. Actual composition varies widely from manufacturer to manufacturer.

4. Polybutylene (PB)

Polybutylene is a recent member of the polyolefin family that includes polyethylene and polypropylene. Although polyethylene is one of the three most common plastics, difficulties in manufacture for polybutylene have kept

costs high and inhibited widespread commercial use before 1973. Because PB resists gradual stretching, or creep, it has good resistance to rupture under pressure, and is chosen as a pipe material for that reason. It also has high impact strength, and a service temperature to 225°F.

The polymer is made by reacting 1-butene with a metallic catalyst in a hydrocarbon diluent, such as heptane or toluene. After the reaction is quenched, the metallic residues may be extracted with alcoholic hydrochloric acid, particularly if the polymer is intended for use as electrical insullation.

PB requires few additives for manufacturing, but is usually heavily protected with stabilizers to give it resistance to ultraviolet light and general weathering. The stabilizers used are the same general class of metallic compounds described for PVC. In some applications, it is necessary to add flame retardant chemicals to polyolefins.

Most impurities from manufacture of the monomer would be low molecular weight hydrocarbons, usually partially unsaturated, such as propylene or ethylene. Presumably some of these compounds are incorporated in the polymer. Other impurities, such as the diluent used in polymerization and the metallic catalyst, remain in the polymer slurry. The degree to which they persist in the finished product depends strongly on the nature of the manufacturing process and on whether the impurities must be removed to maintain physical properties for the intended application. Plastic pipe may not be considered an exacting application for polybutylene.

Since polybutylene, as with most of the polyolefins, is practically insoluble in most common solvents, PB pipe is not joined by solvent welding methods, although it can be fused by heat. This is difficult in the field, and mechanical fittings are most common.

5. Polyethylene (PE)

Along with PVC and polystyrene, polyethylene is one of the three major plastics in use today. PE is the simplest member of the general class of polyolefins, which includes polybutylene.

The plastic is made from polymerization of ethylene gas in reactions similar to those described for PB. The resulting plastic has similar needs for stabilization to protect from light and oxidation. PE has less resistance to heat and shows a tendency to stretch under continuous tension which makes it less suitable for high pressure use or indoor plumbing than PB. PE pipe is mechanically fitted rather than solvent welded.

B. SUMMARY OF TEST RESULTS

In order to determine which chemical substances are actually found as impurities in pipe distributed in California, Thomas Reid Associates contracted with California Analytical Laboratories, Inc., Sacramento (CAL) to analyse the pipe itself. Because of the limited time available, CAL was only asked to provide a qualitative analysis of a few pipe samples. Further work can be done to obtain quantitative estimates of the concentration of potential contaminants in the pipe and of a more broadly representative sample.

The decision to have this laboratory analyze the pipe composition rather than water in contact with the pipe was based on the reasoning that if a compound was not present in the pipe, it could never enter the water supply. With a test of water in the pipe, as with the Montgomery lab study, a negative finding does not rule out a chemical that was in the pipe being in the water as well, since it may represent an analytical difficulty.

Only three types of pipe material were available for test: PVC, CPVC, and ABS. The PVC and ABS samples were obtained from two manufacturers. The results of the qualitative tests indicate significant quantities of a number of compounds which are on the EPA priority pollutant or a formally recognized carcinogens. The CAL results are summarized in Table II-1. The "unknowns" mentioned in the table appear to represent well over half of the mass of low molecular weight impurities in the pipe. Some of the unknowns may be identified with further study, but the range of possible substances which can be in the pipe plastic is so broad that definite identification is nearly impossible.

TABLE II-1

IMPURITIES DETECTED IN ABS, PVC, AND CPVC PLASTIC PIPE

SAMPLE IDENTIFICATION	COMPOUNDS FOUND
Acrylonitrile-butadiene-styrene (ABS)	
Gable Plastics Spartan Plastics	dichloromethane acrilonitrile methyl cyclopropane benzene tetrachloroethene toluene 4-ethenyl cyclohexene ethyl benzene methylethyl benzene hexane styrene propyl benzene 1-methylethenyl benzene unsaturated alkanes 2,6-bis(1,1-dimethylethyl) -4-methyl phenol heptyl phenol unknown (several)
Polyvinyl Chloride (PVC)	
Pacific Western Extruded Plastics Co.	dichloromethane bromochloromethane trichloroethene toluene bis 2-ethylhexyl phthalate DEHP unknown (many)
Chlorinated Polyvinyl Chloride (CPVC)	
GSR	dichloromethane chloroform hexane tetrachloroethene toluene pentachloroethane hexachloroethane bis 2-ethylhexyl phthalate DEHP alkanes (several) unknown (several)

Source: California Analytical Laboratories, Inc. 11/12/80.

20823017

BFG07256

CHAPTER III -- CONTAMINATION

A. GENERAL CONSIDERATIONS

Water will be contaminated by chemicals in the pipe if those chemicals are extracted from the plastic matrix. Several physical and chemical parameters will determine the rate at which substances are extracted. These will be introduced after a simple discussion of the model for substances entering into the water.

Chemical substances in the plastic matrix can leave the pipe through one of two routes: through the water that runs through the pipe, or through the air that surrounds the pipe. The likelihood of a chemical substance escaping into the water depends on its solubility in water; its tendency to evaporate into the air depends on its vapor pressure. Solubility and evaporation will deplete the chemical substance from the thin layer of pipe immediately at the surface. Extraction of the compound from the pipe will continue only if this thin layer is replenished. Chemical substances can diffuse through the polymer matrix, and in this way replenish the surface layer. Diffusion depends on the relative properties of the matrix and the substance. Generally, larger molecules are slower, and molecules which have chemical attraction to the polymer matrix will be retarded. Since the molecules diffuse through the matrix along a gradient of concentration, diffusion is inhibited if the surface layer is not depleted by the water. All of these processses -- solubility, evaporation, and diffusion -- are accelerated by increasing temperature.

These principles allow us to make simple predictions as to the rates at which different chemical substances will be leached from the pipe. Substances with high solubility in water, such as di-methyl formamide (DMF) and methyl ethyl ketone (MEK) will be lost into the water as soon as they reach the surface of the pipe. Other substances, such as the phthalate esters or styrene will be extracted more slowly, based on solubility alone. Since larger molecules diffuse more slowly than smaller molecules with similar chemical properties, one would expect bis-2-ethyl-hexyl phthalate (DEHP) to be leached more slowly than dibutyl phthalate (DBP).

The problem of extraction from solvent-welded joints is somewhat more complex, although the same basic principles apply. With welded joints, the solvent is released into the water from two sources. One is solvent in the welding compound directly exposed to water, particularly in a poorly made joint with excessive cement. The second is gradual migration of the solvent by diffusion through the plastic matrix of the joint or the pipe itself. The two mechanisms will occur at different rates.

The simple model of leaching predicts that the concentration of contaminants in the water will be primarily limited by the rate at which material can diffuse through the polymer matrix and be released. This is true, because solubilization of the organic materials in water is generally far more rapid than diffusion through the plastic. Recognition of the diffusion limitation of the contamination process is important in predicting the resulting concentrations of material in potable water.

The first prediction is that the half-life of a substance in the pipe will vary depending on the substance's chemical composition. For example, ABS plastic is contaminated with acrylonitrile and styrene monomers. Because acrylonitrile is a smaller molecule than styrene and more readily soluble in water, we would predict that it would be extracted more rapidly from the polymer matrix of ABS pipe. Both substances will continue to excape into the water until there is no more monomer remaining in the martix. This means that for equal initial concentrations of acrylonitrile and styrene in the pipe, acrylonitrile will show higher initial concentrations than styrene in the water, and the decline of acrylonitrile contamination over time will be more rapid than that observed for styrene. Thus, the half-life for the acrylonitrile content of the pipe may be on the order of several months, whereas that for styrene may be many times greater.

The second prediction is that concentration of contaminant in the water depends primarily on the amount of time that the water remains in the pipe -- the so-called dwell time. Material will be released into the water as rapidly as it is carried to the surface layer by diffusion in the polymer matrix. Only for highly insoluble materials or for inordinately long dwell times would the concentration of the material in water reach saturation and inhibit further dissolution of the contaminant. Overall, this leads us to expect that the dwell time effect on water concentration will be most apparent over intervals of a few hours to as much as a few weeks, whereas the decrease in dissolution rate due to pipe depletion will be apparent only over a time frame ranging from a few weeks to as much as a few years--depending on the nature of the substance.

Several potential contaminants fall into a special class: those which are created as a result of some process continuing in the pipe in use. Many of the stabilizing compounds used for PVC, PE, and PB pipe are themselves consumed or degraded to new substances in the course of their service. These new substances are also released to the water and may have diffusion or solubility parameters different from the original substance. For these substances, concentrations in the water will depend more on the rate of weathering, and will be seen to increase with exposure to heat or sunlight.

Another group of substances with unusual patterns of appearance are products of chemical reactions between other contaminants in the pipe. Little is known about the role of impurities in reactions occurring slowly in the polymer matrix. For PVC degradation, the chlorine released from the polymer is known to react to form hydrogen chloride, which would itself react immediately with water and appear as an increase in the hydrogen ion concentration, or acidity. There is speculation as to the possibility of residual chlorine in treated domestic water supply reacting with substances in the pipe or released into the water by the pipe. It is difficult to predict the concentration of secondary substances.

B. TEST DATA

For reasons poorly understood there have been no large scale tests of water contamination from plastic pipe. Part of the difficulty is obtaining statistically valid test results that can be applied to the broad problem of public health risk. Not only are there several plastics used for pipe, but there are many manufacturers, and there are important differences in

contamination potential between manufacturers. Furthermore, it is analytically difficult to identify all of the components that may be contaminants in water contained in plastic pipe. Since some of the potential contaminants are known carcinogens, the levels of contamination from these substances must be measured with exceptional accuracy.

For this study, we have one set of water contamination test data -- those compiled by Montgomery Engineers Inc., Pasadena, California, under contract to the Plastic Pipe Manufacturers and behalf on the California Department of Health Services, Hazard Evaluation System. Those data will be referred to as "the Montgomery Data". to our knowledge, this report is the only currently available study of water contamination from plastic pipe.

The Montgomery Data apply only to some tests of PVC and CPVC pipe; no attempt was made to test ABS, polybutylene, or polyethylene pipes contemplated for use in potable water systems in California. Thus, we have no information of any sort on the actual levels of contaminants observed in waters conveyed by those pipe systems not tested by Montgomery.

In considering the Montgomery Data themselves, we first examine the numbers for their statistically significant information content, then we consider the problem of data reliability.

1. Numerical Interpretation of Montgomery Data

Problem of Many Variables and Difficulty of Applying Statistics

Montgomery Labs set up an elaborate series of plumbing simulation systems. The tests examined two different kinds of pipe:

PVC (outdoor)
CPVC (indoor)

three kinds of water:

Pasadena Municipal Water Supply
State Project Water
Colorado River Water

two temperatures:

hot
cold

three primer/cement combinations for pipe welding:

Weld-On P72/713
Weld-On P70/710
Fuse-On NO5/916

two joint qualities:

good
bad

three different types of leaching tests:

static
normal usage situation
kinetic (for solvents)

This array of sampling situations resulted in a large number of water samples requiring analysis. The different test systems entailed varying dwell times from 4 to 336 hours; the water samples are taken at different elapsed time intervals; and there were a series of controls, blanks, and spiked samples taken to validate certain types of analyses.

The numbers themselves show much variation. Little effort apparently was spent in taking replicates which could be used to show whether or not the variation is significant. It is tempting to interpret the variation as somehow reflecting physical phenomena related to the vast number of experimental variables which were addressed in the study, yet without statistical tests as a basis, the interpretation is simply speculation. Considering the analytical and methodological difficulties encountered in the course of the study (dilution problem for solvents, tygon tube for water intake, and running out of non-municipal water for tests), it seems that much of the experimental complexity is overambitious for the first stage of a contaminant study. The lack of replication, the large number of treatments, and the largely asymmetric combination of treatment values frustrates conventional statistical analysis. Nonetheless, the information in the Montgomery data can lead to several important conclusions on the likelihood of contamination of the water supply by plastic pipe.

The first most obvious question to ask is what compounds appear in the water. If all of the various experimental treatments are merely viewed as different approaches to the same question, we see high levels of many of the priority pollutants. Later, we will discuss the significance of the condition under which the high levels appear. Table III-1 shows that hazardous materials such as chloroform and carbon tetrachloride are found at levels up to 146 and 50 ug/l, respectively. DEHP is found as high as 246 ug/l. Common solvents are found at far higher levels, such as n,n-di-methyl formamide at 4,300 ug/l, and methyl ethyl ketone 115,000 ug/l.

Before we address the possible effects of the experimental treatments, the significance of these numbers should be held clear. Levels as high as these were actually observed in samples of water taken from plastic pipe systems. They indicate in at least a qualitative sense possible levels of contamination Apart from the simple observation of contamination, we can examine the different experimental set-ups to see what conditions appear to determine the level of contamination. This is the subject of statistics. There are a number of simple statistical tests which have evolved to aid scientists in evaluating numerical data. In various ways, the tests are tests of significance, that is, whether the numerical results are consistently due to some real relationship between the numbers, or whether they are merely due to random variation or experimental error.

The results of tests are usually expressed as a probability or confidence interval. For example, for a given result we might say that there was a 5% chance that the result could have been obtained by random error; and that leaves us with a 95% confidence in attributing some significant

TABLE III-1

HIGHEST CONCENTRATIONS OF COMPOUNDS TESTED BY MONTGOMERY LABS

Compound	Conc. ug/l	Table	Test
Dichloromethane	29	3-9	Static CPVC/Poor/Hot Pasadena Elapsed: 120 hr. Dwell: 72 hr.
Chloroform	146	3-19	Static CPVC/Poor/Cold Pasadena Dwell: 2 wk.
Carbon Tetrachloride	50	3-19	CPVC/Poor/cold Pasadena Dwell: 2 wk.
Dichlorobromomethane	25	3-12	PVC Static/Colo. R. Raw Water
Trichloroethane	4.0	3-19	PVC/Good/State Project Dwell: 2 wk.
Dibromochloromethane	28	3-12	PVC Static/Colo. R. Elapsed: 24 hr. Dwell: 24 hr.
Bromoform	2.6	3-12	PVC Static/Colo. R. Elapsed: 24 hr. Dwell: 24 hr.
Tetrachloroethane	9.7	3-19	Static CPVC/Good/Hot Pasadena Dwell: 2 wk.
Hexachloroethane	D	3-8,9,10,11,12	
Pentachloroethane	D	3-8,9,10,11	
Benzene	0.5	3-13	Kinetic: Weld-On 48 hr. Kinetic: Fuseon 48 hr.
Toluene	41	3-13	Kinetic: Fuseon 120 hr.
Chlorobenzene	0.2	3-8	Static CPVC/Good/Hot Pasadena Elapsed: 148 hr. Dwell: 4 hr.
Ethylbenzene	2.7	3-13	Kinetic: Fuseon 120 hr.
p-Xylene	2.5	3-13	Kinetic: Fuseon 120 hr.
o,m-Xylene	1.3	3-13	Kinetic: Fuseon 120 hr.
Propyl benzene	ND		
Methyl ethyl benzenes	ND		
Trimethyl benzenes	ND		
Phenol	33	3-13	Kinetic: Weld-on 2 hr.
Methylethyl ketone	115,000	3-1	Static CPVC/Poor/Cold Pasadena 2 wk.
Tetrahydrofuran	375,000	3-2	Static CPVC/Poor/Cold Pasadena 2 wk.
Cyclohexane	13,000	3-3	Static CPVC/Poor/Cold Pasadena 2wk
n,n-Dimethylformamide	31,000	3-6	Kinetic: Weld-on P70/P711 120 hr.
Dibutyl phthalate	77	3-14	Kinetic: Fuseon 2 hr.
bis(2-Ethylhexyl)phthalate	246	3-11	Static CPVC/Good/Cold Water Elapsed: 144 Hr. Dwell: 24 hr.
n-Nitrosodiphenyamine	27	3-10	Static CPVC/Good/Cold Pasadena Elapsed: 2 wk. Dwell: 336 hr.

Source: Montgomery Engineers Data

relationship to the numbers. This point is not of purely academic. The Montgomery Data contain a lot of numbers. In interpreting those numbers it is important to know how much confidence can be placed on relationships which the numbers appear to demonstrate. It is not adequate to "eye-ball" a few numbers and discern a trend. That trend must be proven statistically.

Too Few Data Points

Statistical tests of the Montgomery Data are difficult, however, because few of the experimental variables have more than two or three data points. Recall that a line may always be drawn between two points, but the more points there are, the more difficult it is to establish where a line should be drawn which best fits all of them. This difficulty is demonstrated by the problem of attempting to see whether "good" and "bad" joints affect the concentration of chloroform in two week static samples (refer to Montgomery Table 3-19). When cold water is used, chloroform is found in the good joint test at 78 ug/l. In the poor joint test, the level is found to be 146 ug/l. From these two numbers alone, one might infer that the poor joint led to the greater contamination. This conclusion cannot be supported by statistical analysis, because we have no idea how much variation there could be among several samples of poor joints or good joints alone.

When we look at the hot water in the same set-up and find the good joint value (92 ug/l) exceeds the poor joint value (69 ug/l), and we suspect that the joint quality may not be an important determinant of chloroform concentration after all. Many more replicates of each type of joint and water temperature might have clarified the true relationship between the variables.

The danger in statistically inadequate data sets is the temptation to infer relationships that are supported by nothing other than intuition, but appear to be matched by the numbers. For example, it is intuitively appealing to think that a poor joint will lead to higher levels of contamination than a good joint. Looking at the Pasadena-cold data alone, someone might be tempted to state that the Montgomery Data support that theory. Actually, that level of support is mere coincidence. Most of the treatments in the study outlined earlier will not allow any valid inferences regarding either the safety of plastic pipe nor mesures to reduce contamination hazard to the user (eg. flushing the pipe before use.)

The Data Do Not Support the Hypothesis that Flushing Reduces Contaminant Levels

Re-examination of the Montgomery data clearly shows that there is no statistically significant evidence that flushing reduces contaminant levels in the water. The Montgomery report appears to show that as the pipe aged and as water ran through it the levels of many contaminant substances declined. This lead to a proposal to use flushing and some probationary period in order to eliminate public health hazard. The provisional acceptance of plastic pipe in the HES report was based on the authors' belief that the hazard could be reduced by flushing.

The test which appeared to show that flushing and aging reduced hazard measured contaminant levels after various combinations of elapsed time (pipe aging) and dwell time (time water stood in the pipe). There were two problems with this approach. One is that elapsed time and dwell time are independent

variables, and should have been tested separately as well as combined. The second is that in the experimental design used, for some unexplained reason, dwell time was varied inversely with elapsed time -- that is, the older the pipe, the shorter time a sample of water was left in it before measurements were taken. The first or "0-hour" sample was water that had stayed in the pipe for 336 hours (2 weeks). The elapsed time for subsequent samples is measured from the end of that two-week initial period. The 24 and 48 hour samples each have 24-hour dwell times. Then the sample taken after 120 hours of elapsed time was left in the pipe for 72 hours, perhaps over the weekend. The next sample, at 144 hours, was left in the pipe for only 24 hours; and the final sample at 148 hours, was left in the pipe for only 4 hours.

If the reader observes only elapsed time, the change in concentration of chloroform and other important substances appears to diminish over the course of the study. This suggests that flushing would be an appropriate way to reduce contamination. In attempting to discern the true meaning of the data, we have applied statistical tests, as described below, to separate the effects of dwell time from the effects of elapsed time, and to better understand what really happens when the two effects are combined.

In order to improve the statistical testability of the data, we have combined many of the treatments into one class; namely, we have assumed that the variation, if any, caused by the experimental treatments of CPVC vs. PVC, good joints vs. poor joints, hot water vs. cold water, and Pasadena vs. State Water Project or Colorado River Water are independent of the effects of elapsed time and dwell time. This assumption is probably a good one, since there is no a priori reason to suspect that the experimental treatments and the time treatments should be related. If they are independent, then we may lump the data to obtain a larger sample, which makes for a better statistical test. In this way, we have examined the static test results using a total of 34 data points to represent six combinations of dwell times and elapsed time.

Our statistical test is a linear regression of concentration of contaminant against time -- one linear regression against elapsed time, a second linear regression against dwell time. A linear regression is a test to see if there is a significant functional relationship between a dependent variable (concentration) and an independent variable (time). When these regression lines are computed, only dwell time turns out to be a statistically significant predictor of contaminant concentration. Dwell time turns out to be a highly significant (at the 99.9% level or greater) predictor for every contaminant (four solvents and all the haloalkanes).

On the other hand, there appears to be no significant functional relationship between elapsed time alone and contaminant concentration in the water.

To understand the combined effect of elapsed time and dwell time, we performed a multiple linear regression on the 34 data points. This test gave a highly significant fit of the data to a straight line (ie. a straight line in three dimensions, since there are two independent variables and one dependent variable). It is instructive to see the slope that the analysis assigns to the two variables. As shown in Table III-1, the sign of the slope contributed by the variable "dwell time", is positive, meaning that an increase in dwell time increases the concentration. The slope for the variable "elapsed time" is negative; increasing elapsed time does diminish the

concentration. The relative magnitude of the slopes, however, indicate something of the speed with which this will happen, since both dwell time and elapsed time are measured in hours. For chloroform, for example, the slope ratio is a factor of 50, meaning that chloroform increases water in the pipes 50 times faster than it is eliminated through continuous flushing. This implies that water standing in the pipes, even several years after installation, could over a period of several weeks, attain the same concentrations as when the pipes had been freshly installed and the water had stood for only several hours.

TABLE III-2

CONCENTRATION AS A FUNCTION OF ELAPSED TIME AND DWELL TIME

Compound	a	b elapsed	c dwell	r
solvents (concentration units mg/l)				
methylethyl ketone	-3.4366	-0.030	0.237	0.9483
cyclohexanone	-3.4366	-0.030	0.237	0.9483
dimethyl formamide	-0.0455	-0.001	0.004	0.5589
tetrahydrofuran	-6.3988	-0.071	0.541	0.8192
haloalkanes (concentration units ug/l)				
haloethenes	4.7926	-0.005	0.005	0.2934
chloroform	16.3	-0.003	0.151	0.6431
carbontetrachloride	2.2869	-0.007	0.059	0.6621

N = 34
a - z-intercept
b - slope of x; concentration units per hour elapsed time
c - slope of y; concentration units per hour dwell time
r - correlation coefficient;
all values significant: P greater than 99.9%

Source: multiple linear regression by Thomas Reid Associates of Montgomery Engineer's data

The foregoing discussion notwithstanding, a much longer term test -- on the order of months or years -- would be necessary to be commensurate with the real time scale at which flushing is actually effective. Because some of the substances of concern can be harmful at very low doses, we must have a real

measure of the time it takes for their concentrations to drop to non-hazardous levels. For carcinogens this may mean total absence, which may never be achieved.

2. Montgomery Data Reliability

The reliability question can be examined from two perspectives. First, what is the likelihood that the levels recorded underestimate actual concentrations; and second, what is the likelihood that numbers observed overestimate actual concentrations. In statistics, this duality is known as the Type I and Type II error problem. Unfortunately, the data are not collected with sufficient replication to be amenable to customary statistical analysis. Rather, we are limited to intuitive or anecdotal interpretations.

Problem of Fluctuating Phthalate Levels

One of the more serious concerns is over the levels of phthalic acid esters: DEHP and DBP. Levels of the phthalates fluctuate sharply from no detection (zero), up to 200 micrograms per liter (ug/l). The levels do not appear to fit a pattern and suggest analytical difficulty. On the one hand, they may come from some source external to the experiment; it has been suggested that tygon tubing used to connect the experimental set-up with the water supply is the source of the phthalate contamination. On the other hand, the fluctuation may represent a difficulty in consistently analyzing for DEHP and DBP in the water samples.

The data cast doubt on the suggestion that extraneous tygon tubing alone explains the levels of phthalate acid esters in the water. Although tygon is a PVC compound with high levels of plasticizer, the data do not show consistent ratios between the DBP and the DEHP that would be expected if that simple source of potential contamination were involved. Since exactly the same piece of tygon tubing was in use in a similar fashion in all incidents, one would expect the ratio of plasticizing compounds to be consistent and to match the ratio of plasticizing compounds actually used in tygon tubing. This appears not to be the case.

The phthalates are quite insoluble in water. The extensive health literature on phthalates reviewed in Chapter IV includes several articles which discuss the difficulty of accurately establishing phthalate exposure in the experimental procedures due to the poor solubility of the phthalates themselves. Several researchers have discovered that the phthalates are active in the form of micelles, or an ultrafine dispersion of non-polar, insoluble material in water. In this form, the material appears to be highly biologically active, since it is readily taken up by the lipophilic tissues of living animals. However in the micellular form, it may be difficult to accurately and consistently analyze the presence of the phthalates in the water. Furthermore if phthalates are present in the pipe and being released into the water as micelles, this process will not show the conventional linear response of normal dissolution.

As the data stand, they show occasional high levels of phthalates. The lack of consistency may be the result of an analytical difficulty that would require careful study. Even if the tygon tubing used in the experimental set-up contributed some level of phthalates to the system, it should not be assumed that it accounts for all of the phthalates observed, since it is

quite likely that the plastic pipe system under test can contribute some phthalates. The few high-level values should be the ones used in interpreting the potential health hazard of the system.

Problem of Resolution of Many Compounds

It is far easier to make decisions based on concern about compounds that show occasional but not consistent values than it is to deal with those compounds for which no values are recorded at all. Except for the four solvents, the only other compounds tested were those selected in advance from the U. S. Environmental Protection Agency (US-EPA) Priority Pollutants List. Analytical methods for the priority pollutants are reasonably well established for the gas chromotograph/mass spectrometer (GC/MS) used by Montgomery Labs. The GC/MS entails at least partial separation of components in a mixture in The modern equipment uses computer programs to help match the mass spectra with the known spectra of important or priority pollutants. The method works best when there are relatively few and known compounds to analyze. When there are a large number of chemically similar compounds, particularly if several are present at high levels, the analysis is more difficult and there is the chance that some of the important, low-level compounds may be masked by other substances.

Problem of Solvent Interference

One problem for Montgomery Labs was that the high levels of solvent in the water impaired the analysis of volatile organic compounds. In the draft report, in fact, the levels presented for the volatile organics were considered unreliable in most instances because there were high levels of solvent. Subsequently, some of the chlorinated hydrocarbons were analyzed wth a different technique. From examining the data as published, it is difficult to know whether important compounds such as vinyl chloride were obscured by these analytical difficulties. It is not clear whether the full range of material including vinyl chloride was subjected to the second analytical procedure instituted to overcome the earlier dilution problem with the solvents.

Problem of Unanalyzed Substances

Further, there is usually some significant volume of "residual" material in an analysis such as conducted by Montgomery, which is not readily identifiable and whose constituents may not even be among the priority pollutants. The Montogomery report contains no discussion as to the quantity of this material and there appears to have been no attempt to identify substances outside of the simple list presented in their series of tables. Unfortunately, not all hazardous materials are restricted to the EPA list. There are substances which are known to be used as additives in plastic which may have contaminated the water, yet were not identified by Montgomery.

Problem of Chloroform

Chloroform, and other halomethanes, was detected in the raw water used for filling the piping system. The levels in the plastic pipe system, however, are significantly greater than those in the raw water. This is not surprising since chloroform and other similar chlorinated organic compounds may be used in the manufacture of CPVC pipe, and indeed are found in the pipe.

It has been suggested that the chloroform was formed on standing by reaction of residual chlorine from domestic water supply chlorination with other organic material in the water. For example, hypochlorite ion (OCl^-) reacts with methyl ketones to form chloroform. Considering that the domestic water itself has been heavily chlorinated and de-chlorinated to remove odor and bacterial contamination, there would be little organic material with residual chlorine demand in the water by itself. The most likely source for organics that could enter into a reaction with chlorine are the organic materials which escape from the pipe itself. Even if the chloroform were secondary -- produced by reaction in the water -- it would constitute an independent health hazard due to the use of plastic pipe for water supply.

In fact, it is unlikely that the chloroform observed is secondary or reaction chloroform. The reaction whereby hypochlorite ion oxidizes methyl ketone groups to chloroform is base-catalyzed. At neutrality or pH 7, the half-life of even a reactive substance such as acetone is on the order of 7500 hours. Only strongly alkaline waters, or unusually reactive materials from the pipe could account for the chloroform levels recorded by the Montgomery Studies. There is no evidence for those unusual conditions and we must conclude that the chloroform comes from the CPVC pipe.

IV. POSSIBLE EFFECTS ON POPULATION AT RISK

A. POPULATION AT RISK

If plastic pipe is approved for installation for potable water supply the population at risk will be all of the occupants of new homes outfitted with plastic pipe. Since thousands of dwellings are added to the statewide housing stock each year, this population will comprise thousands or millions of individuals of all ages and both sexes. In considering the problem of exposure to any class of potentially harmful chemicals, there are definite differences in sensitivity between different members of the population at risk. The following ranking indicates generally increasing sensitivity:

Least sensitive	Adult males under 65 years of age
	Adult females 45 to 65 years of age
	Males and females over 65 years of age
	Adult females of childbearing age (15-45)
	Children 6 to 14 years of age
	Children 3 to 6 years
	Infants and children under 3 years of age
Most sensitive	Pregnant women

While individual categories within this list may be exchanged, there is a general increase in sensitivity between the top and the bottom of the list.The meaning of this rank order is that the more sensitive members of the population may tolerate far smaller doses of the offending chemicals without significant adverse health effects. Unlike drugs which are intended for consumption in highly specific doses and rigidly controlled, consumption of chemicals in the domestic water supply introduced via the piping system of individual dwellings is not dose controlled. Although small children, for example, may consume less water than the adult members of a household, they may receive a greater overall dose of these compounds in proportion to their body weight and physiological tolerance. Young children may also be more sensitive to the harmful effects of these chemicals because they will be exposed while their bodies are still rapidly growing and developing, and because the time of exposure and the time for adverse effects to manifest themselves will extend over many years.

The concern for pregnant women is really an extension of the concern for young children. It is now known that most drug and other non-nutritive substances can cross the placental barrier and exert an effect on the developing embryo or fetus. Many of these substances can exert subtle or gross (teratogenetic) changes in normal development and can produce different, though uniformly harmful effects at different stages of pre-natal life. In addition, because of its minute size and the immaturity of its bodily functions -- such as the immune system -- a fetus may be markedly affected by the dose of a substance which has only a minimal effect on its mother.

It is important to stress that the population is at risk not by choice, but simply because they purchased or rented a home built after a certain date. While some may be alerted to the fact that their water supply pipes may pose some sort of risk because of manufacturer's instructions to flush them out after the water has been shut off for some length of time (eg. a two-week vacation), most will have no concept of either the range nor potential health

effects of the substances they ingest with their drinking water. The entire population will have been unwittingly made subjects for a long-range experiment in human toxicology.

B. EXPOSURE

A population consuming a domestic water supply is exposed to the effects of any contaminant substances within that supply in a number of ways. The most obvious is by drinking the water directly. While the amount of "tap water" people consume in preference to other beverages may be small, and is highly variable among the population, there are many other avenues by which people consume drinking water, including using the water for cooking vegetables, meats and grains, and for coffee, tea, reconstituting frozen drinks, and ice cubes, to name a few. The average per capita consumption of drinking water through all uses is one to two liters per day.

People are also exposed to substances in their domestic water supply in bathing and laundry. While very little water is absorbed through the skin, skin-absorptive chemicals present in the water may be taken into the body this way. If these chemicals bind to the fibers of clothing or react with laundry detergents or soaps to form other chemicals whose residues are left on clothing, then home laundry becomes an additional avenue of exposure. The recent major controversy over TRIS flame retardant in children's sleepwear is a case in point of a proven carcinogenic chemical in clothing which can be absorbed through the skin. Most of the chemicals of concer in this survey are lipophillic and likely to be absorbed through the skin.

Drinking water and much of the additional domestic water supply used for bathing, dish-washing, laundry, and to dispose of waste, eventually becomes part of domestic wastewater. The same chemicals present in the water supply because of contact with the plastic pipe will also be present in wastewater. While domestic wastewater does not pose a direct health threat to the human population, since even tertiary-treated wastewater is not used for human consumption, it can pose a hazard to aquatic life and the environment as a whole. There are government standards for permissible levels of organic compounds in waste treatment plant effluent, which are incorporated into the specific provisions of its National Pollution Discharge Elimination System (NPDES) permit. However, low molecular weight organic compounds such as those of concern in the study of plastic pipe are among those most difficult to remove by conventional sewage treatment.

The aquatic environment already receives a substantial load of pollution by both chlorinated and non-chlorinated organic compounds from domestic and industrial wastewater, urban runoff and agricultural (ie. pesticide) drainage. A portion of air pollutants also end up in water or in living organisms in proportion to their solubility and partitioning within the water environment. (For example, some relatively insoluble organics are adsorbed onto small sediment particles within the water and may be ingested by filter feeding animals such as plankton (EPA Regulation, 1980)). The contribution of organic compounds from plastic pipe used for domestic water supply would represent an increase in the organic pollution load from all sources. Since ABS pipe is already in use for drain-waste-vent systems, residential plumbing is already making some contribution to water pollution by organic compounds. The additional pollution caused by plastic water supply piping may be only a

slight increase in the existing organic chemical contamination of surface water. Nonetheless, it is important to give consideration to this aspect of a new source which will definitely add to an existing pollution problem.

C. TYPES OF EFFECTS

1. Background

Most of the chemicals of concern in this study have been subjected to some degree of testing for either their potential for toxicity to humans or for environmental pollution. Tests for hazard to human health come under the heading of "Toxicology studies" and are primarily concerned with relatively short-term exposure to high levels of these compounds.

Toxicology studies attempt to establish one or more of the following adverse health effects of substances:

(1) Acute toxicty: symptoms of poisoning -- respiratory distress, nausea and vomitng, headache, nervous system depression or activation, cardiac difficulties.

(2) Chronic toxicity: longer term damage to organs or the nervous system; histological changes in cells or tissues, cell death (necrosis)

(3) Carcinogenesis: causing malignant tumors, benign tumors suggestive of later or concommitant malignant change, or pathological changes in cells associated with change from the normal to the malignant state.

(4) Teratogenesis: causing fetal malformations or fetal death.

(5) Mutagenesis: causing genetic mutations in cell genetic material (DNA, RNA); closely associated with carcinogenesis and teratogenesis.

Most studies of effects (1) through (4) utilize small, mammalian laboratory animals (mice, rats, rabbits -- sometimes cats, dogs, monkeys, ferrets, etc.) as somewhat similar to humans, and because they are economical to rear in laboratories, have short life spans, rapid reproduction and breed readily in captivity. Even with all these advantages, the limitations of time to conduct experiments and to wait for substances to act make it virtually impossible to simulate with laboratory populations the subtle but cumulative toxic effects of the extremely long-term, low-level chronic exposure to which human populations are subjected. Typically, the substances to be tested are administered to the test animals via injection,ingestion, inhalation, or applied to the skin. The doses administered are often several orders of magnitude higher than the expected level of human exposure, particularly in studies of carcinogenesis. In general, the interpretation of animal test results is that if any tumors (in excess of "background") are found in the laboratory animals, then the substance must be regarded as potentialy carcinogenic in humans, even with the dose factor taken into account.

Since many of the test animals used to not live long enough, or naturally encounter toxins or carcinogens, the natural incidence of cancer in these animals is extremely low -- sometimes too low to allow a statistically significant sample of the test animals to manifest the disease after laboratory treatment. That is, physical facilities, labor cost, and other limitations of experimental design make it impossible to conduct the test on a lab population large enough to detect the effect of interest (e.g., the test must be run on 50 animals when one needs 50,000). To alleviate this problem, tests may be run on specially developed strains of rats or mice which have been selected to be extremely sensitive to carcinogens and are enriched in the incidence of "background" cancers.

Recently, a test was developed for detecting carcinogenesis using specially developed strains of a bacterium Salmonella typhimurium, which have lost the ability to repair DNA present in all normal living cells, and thereby suffer an unusually high rate of mutation. The Ames test, named for its originator, Bruce Ames of the University of California at Berkeley has provided a great advance in sccreening potential mutagens and carcinogens. Mutation is ordinarily an extremely slow process, affecting only about one cell in 10,000 in a higher organism such as a mouse or man. Since many mutations also result in the demise of the mutated cell, it takes an extremely long time for the effects of multiple mutations to be detected as something like a cancer in a higher organism -- on the order of years or decades. Bacterial "individuals" are single cells and experience extremely high growth rates so that from a single cell billions of offspring may be produced within a few hours. Since they are also of minute microscopic size, billions may be present on a single culture plate. Thus, bacteria inherently offer many advantages over larger organisms in the study of mutation, since a population large enough to detect extremely low frequency effects may be readily observed.

Studies of environmental pollution have identified criteria for organic chemicals liable to cause serious environmental problems. These criterial are applied when an exmaination is made of the potential of a chemical of interest to be a major cause for concern. Among these criteria are the following:

(1) From toxicology studies (as above) is the chemical known to be toxic, carcinogenic, mutagenic and/or teratogenic?

(2) Is the chemical selectively partitioned and accumulated in living systems? For example, many organic compounds have very low solubility in water, but high solubility in fat, and are readily absorbed in the gut of animals. From this point they may accumulate in the liver or other tissues to many thousands times the level at which they are found in the non-living environment (water or soil).

(3) Is the chemical persistent, or are any of its breakdown products peristent? Persistence means that the chemical does not degrade either chemically or through bacterial action ito harmless substances. In at least one study DEHP was shown to have a half-life greater than one year (Jungclaus et al, 1978), and substances such as DDT may persist in the environment essentially unchanged for decades.

(4) Does the chemical interact with the environment so as to be transported over long distances and is it able to affect at large proportion of the world's ecosystems? Quite a number of organic compounds, including dialkyl phthalates (Jungclaus, 1978; Office of Toxic Substances, 1978) and tributyl tin oxide have been shown to adsorb strongly to fine dust particles in air or soil particles in the aquatic environment and thus be capable of transport over long distances and able to be ingested by living organisms during either respiration or feeding.

2. Observed Effects of Those Chemicals Found in Water from Plastic Pipe

A preliminary review of the toxicology and environmental pollution literature of the compounds potentially released to the water supply from plastic pipe -- namely, plasticizers, solvents, stabilizers and impurities has revealed that none of them are devoid of some potentially serious adverse effects. A summary of the findings of this literature review is shown in Table IV-1; more extensive documentation of these findings is given in Appendix B.

TABLE IV-1

SUMMARY OF FINDINGS FROM PRELIMINARY LITERATURE REVIEW

Compounds	Acute Toxicity	Chronic Toxicity	Mutagenesis Carcinogenisis	Teratogenesis or Fetal Death
Plasticizers				
DEHP	Y	Y	Y	Y
other phthalates	Y	Y	Y	Y
Solvents				
DMFA	Y	Y		
Methyl ethyl ketone	Y	Y		
Cyclohexanone	Y	Y		
Tetrahydrofuran				
Stabilizers				
N-NDPA		Y	Y	
other nitrosamines			EPA List	
Impurities				
CCl_4	Y	Y	EPA List	
Chloroform			EPA List	
Monomers				
Acrilonitrile			EPA List	
Styrene			EPA List	
Vinyl chloride			EPA List	

Key: Y = Yes; EPA List = Formally recognized carcinogens
Source: Organic Syntheses, vol. 58;
Appendix B - Toxicity Literature Review Summary

Table IV-1 shows that the phthalate plasticizers have shown acute and chronic toxicity, mutagenic/carcinogenic and teratogenic activity. The solvents have definitely been shown to have toxic effects; the stabilizer N-Nitrosodiphenylamine has demonstrated chronic toxicity and likely carcinogenesis. A number of the impurities -- notably carbon tetrachloride and chloroform are toxic and are on the EPA list of known carcinogens.

The documentation from the EPA PMN Regulation to prohibit licensing new substances chemically similar to other phthalate plasticizers now in use cites numerous studies showing that alkyl phthalates fulfill all of the criteria listed above for serious environmental contaminants-- toxicity, bioconcentration potential, persistence and widespread dispersion potential.

Department of Health Services HES report noted that methyl-ethyl ketone (a solvent) is a neurotoxin and a nervous system depressant and that DMF (a solvent) causes liver and pancreatic damage. In view of the stated risk posed by these compounds, the tendancy of HES report toward acceptance of the pipe was reliance on observation in the Montgomery lab results that made it appear that the toxins were flushed out, and that their concentration diminished with time. While not stated explicitly by HES, it was apparent from their conclusions and recommendations that they felt that assurances that the pipe would be flushed out before use was a necessary condition to assure that contaminants in the pipe dropped to safe levels. The apparent decline in toxic substance concentration in the Montgomery data is not statistically significant (see Chapter III).

The Montgomery data do show very high levels of chloroform, carbon tetrachloride and trichloroethylene, which are EPA recognized carcinogens. In addition, other substances known or suspected to be in pipes not tested by Montgomery are carcinogens (see Table IV-2). The EPA has published proposed standards for some of these substances in drinking water. The levels are those estimated to adaquately protect public health, not the same a previous published levels which represented only the levels that could be attained by existing technology for municipal water supply treatment of polluted water.

The levels seen in water from plastic pipe are severa hundred fold greater than levels projected to cause one cancer death in one million persons exposed per year. A linear dose-response relationship would imply several hundred cancer deaths per year from a million persons using water with the observed high levels of carcinogens such as chloroform. The actual hazard is impossible to predict because we cannot take into account the synergistic effect of the many toxic substances acting together, nor do we know the long term, time integrated dose that people will recieve. Given the present level of uncertainty regarding what chemicals and how much of each chemical is involved, it is best to view the EPA levels as a warning that a significant health hazard exists for at least these several substances.

TABLE IV-2

LIKELIHOOD OF CONTAMINATION BY FORMALLY RECOGNIZED CARCINOGENS

Compounds	Expected (used in mfg)	Found in Pipe[4]	Found in Water[5]
OSHA list of Carcinogens[1]			
2-Acetylaminofluorine			
4-Aminobiphenyl			
Benzidine			
3,3'-Dichlorobenzidine			
4'-Dimethylaminoazobenzene			
alpha-Naphthylamine			
beta-Naphthylamine			
4-Nitrobiphenyl			
N-Nitrosodimethylamine			
beta-Propiolactone			
bis-(chloromethyl)ether			
Chloromethyl methyl ether			
4,4'-Methylene-bis(2-chloroaniline)			
Ethyleneimine			
Asbestos[2]			
Benzene[2]		Y	Y
Coal tar volatiles - coke oven emissions[2]			
Vinyl chloride[2]	Y		
Strong Carcinogens[2]			
Benz(a)pyrene			
2,4-Diaminotoluene			
Dimethylcarbamoyl chloride			
1,1-Dimethylhydrazine (and salts)			
Dimethyl sulfate			
Hexamethylphosphoramide			
Hydrazine (and salts)			
N-(2-Hydroxyethyl)ethyleneimine			
Methylhydrazine (and salts)			
2-Nitronaphthalene			
Nitrosoamines	Y	?	Y
Propane sultone			
Propyleneimine			
Experimental Carcinogens[2]			
Acrilonitrile	Y	Y	?
3-Amino-1,2,4-triazole			
Carbon tetrachloride		Y	Y
Chloroform	Y	Y	Y
1,4-Dichloro-2-butene			
Dioxane			
Epichlorohydrin			
Ethylene dibromide			
Ethylenethiourea			
Lead chromate			
Methylenedianiline			
Styrene	Y	Y	?

Tetramethyl thiourea			
Thiourea			
o-Toluidene			
Trichloroethylene	Y	Y	Y
Vinylcyclohexene dioxide			
Zinc chromate			

Key: Y=Yes; ?=Not tested
Sources:
1. Organic Synthesis, Vol. 56, p. 128.
2. Organic Synthesis, Vol. 58, p. 168-169.
3. T.R. Crompton, Chemical Analysis of Additives in Plastics.
4. CalLabs report, November 12, 1980.
5. Montgomery Lab report, August 1980.

---

3. Hazard Assessment

Combining the considerations given in Section IV-A "Population at Risk" with those in IV-B "Exposure" and IV-C 1. and 2. "Background" and "Observed Effects" raises the ultimate question of concern -- what will be the effects of using plastic pipe for domestic water supply on the population at risk, and who will assume the responsibility for the harm that can come from such use?

We have the conservative interpretation of the Montgomery data showing occaisionally high values of toxic substances in the water from some types of pipe, and the qualititative test results from California Analytical Labs (November, 1980) It is clear that a sensitive population may be exposed for a tremendous length of time to uncontrolled and potentially damaging levels of toxins and known carcinogens. In addition, these compounds will add to the local and global load of environmental contamination in a potentially significant, yet in an uncontrollable and unpredictable amount.

It is the uncontrollability and unpredictability of the risk to both human health and the environment which must give rise to an argument of caution. Too often in the recent past we have learned too late from our mistakes that products the chemical industry protested were safe were disastrous to health or the environment on an unprecedented world-wide scale. Examples are numerous. The predecessor plasticizer to the alkyl phthalates - PCB was withdrawn from use only after billions of pounds had been manufactured and inflicted on the environment, and only after yet unreckoned damage had been done. Carcinogenesis, chronic toxicity to man and animals, concentration in food chains, thin eggshells, bird extinctions are only a partial list of the effects which came to be associated with PCB and related chemicals such as the DDT group of pesticides.

Too often, as well in attempting to rectify one problem a more damaging one will be created by a well-meaning but not adequately informed public body. In a rush to and save children from death in home fires, the U.S. Government set a deadline to make all children's sleepwear flame-retardant. The chemical industry's response was the mass introduction of TRIS-treated sleepwear into the market. Whether for economic or technological reasons TRIS was the chemical industry's chemical of choice. Only later did it become widely known

that TRIS was absorbed through the skin and a definite carcinogen. This compound was withdrawn from the market after millions of young children had been exposed to a needless and unknown risk of later contracting cancer. Other tri-phosphates related to "TRIS" are used as stabilizers and plasticizers for PVC (see Appendix A).

The question of dose and the sensitivity of the receiving population is especially instructive. Drugs are an obvious class of compounds which at some doses are hoped to have a therapeutic effect, but can be harmful or even lethal at other dose levels. In the process of drug certifications, the U.S. Government (FDA) has a formal protocol published in CFR Title 21 Section 312 and ff for submission of information to allow that agency to make a decision regarding safety and licensing. Dose and sensitivity are especially important in that in a drug intended for use by a sensitive segment of the population such as pregnant women, much more extensive data regarding possible teratogenicity etc. will be required for agency review before licensing than for a drug intended for the general population. Drugs in general carry caveats about the safety of use in young children, pregnant women and persons with particular health conditions. Once licensed, the distribution and consumption of these substances is rigorously controlled through the prescription process. It seems inconsistent that government can on the one hand take such pains to regulate some substances which are potentially harmful when uncontrolled, and yet on the other hand allow these same sensitive individuals to ingest a whole class of strongly implicated harmful compounds (from plastic pipe) in uncontrolled amounts, over an indefinite time period.

At present, the data concerning the chemicals in the pipe, the levels leached over time into the water supply and health effects on the population and the environment are incomplete and inconclusive. What evidence there is, such as presented in this report indicates that the chemicals are toxic, the levels are harmful, and the risks are real. In the absence of conclusive information to the contrary, a blanket decision to license PVC, CPVC, ABS, polyethylene, and polybutylene pipe for domestic water supply cannot reasonably be made.

APPENDIX A -- KNOWN PLASTIC CONSTITUENTS AND COMMERCIAL ADDITIVES

The polymer industry makes use of hundreds of chemicals in manufacture of commercial plastics. The following pages list several classes of additives to illustrate the range of substances that may be in plastic pipe. The significance is twofold: 1) these substances complicate the analytical problem of analysing what is in a pipe sample or in water from a pipe, and 2) these substances may not have been subject to adaquate toxicological screening.

The lists are taken from T.R. Crompton Chemical Analysis of Additives in Plastics 2nd edition, 1977 Pergamon Press, New York.

Antioxidants

1 Topanol A	2,4-Dimethyl-6-t-butylphenol
2 Topanol OC	2,6-Di-t-butyl-4-methylphenol
3 Tenox BHA	Mixture of 2- and 3-t-butyl-4-hydroxyanisole
4 Binox M	Bis(3,5-di-t-butyl-4-hydroxyphenyl) methane
5 Ionox 330	1,3,5-Trimethyl-2,4,6-tris-(3,5-di-t-butyl-4-hydroxybenzyl)benzene
6 Nonox WSP	Bis(2-hydroxy-3-α-methyl-cyclohexyl-5-methylphenyl)-methane
7 Nonox WSL	2,4-Dimethyl-6-α-methyl-cyclohexyl-phenol
8 Nonox DCP	2,2-Bis(3-methyl-4-hydroxyphenyl) propane
9 Calco 2246	Bis(2-hydroxy-3-t-butyl-5-methyl-phenyl)methane
10 Topanol CA	1,1,3-Tris(2-methyl-4-hydroxy-5-t-butylphenyl)-methane
11 Santonox R	Bis(2-methyl-4-hydroxy-5-t-butylphenyl) sulphide
12 Topanol TP	Bis(2-hydroxy-3,5-di-t-butyl-6-methylphenyl)-sulphide
13 Suconox 18	N-Stearoyl-p-aminophenol
14 Naugawhite	Bis(2-hydroxy-3-nonyl-5-methyl-phenyl)methane
15 Agerite Superlite	-
16 Voidox 100%	2,6-Di-t-butyl-4-methyl phenol + sorbitan/fatty acid compound
17 Irganox 1010	Pentaerythritol-tetra-β-(3,5-di-t-butyl-4-hydroxy-phenyl)propionate
18 Irganox 1076	n-Octadecyl-β-(3,5-di-t-butyl-4-hydroxyphenyl)-propionate
19 Irganox 1093	Di-n-octadecyl-3,5-di-t-butyl-4-hydroxybenzyl phosphonate
20 Polygard	Tris(nonylphenyl)-phosphite
21 Nonox CI	N,N'-Di-β-naphthyl-p-phenylenediamine
22 DLTDP	Dilaurylthiodipropionate
23 Salol	Phenylsalicylate
24 Cyasorb UV9	2-Hydroxy-4-methoxybenxophenone
25 Cyasorb UV 531	2-Hydroxy-4-n-octoxybenzophenone
26 Uvinol 400	2,4-Dihydroybenzophenone
27 Cyasorb UV 24	2,2'-Dihydroxy-4-methoxybenzophenone
28 Tinuvin P	2-(2'-Hydroxy-5'-methylphenyl)-benzotriazole
29 Tinuvin 326	2-(2'-Hydroxy-5'-t-butylphenyl)-3-chlorobenzotriazole
AgeRite Alba	Hydroquinone monobenzyl ether
AgeRite Spar	Styrenated phenol
AgeRite Superlite	A polyalkyl polyphenol
Antioxidant 5	Not disclosed
Antioxidant 425	2,2'-Methylene-bis (6-tert-butyl-4-methylphenol)
Antioxidant 2246	2,2'-Methylenebis (6-tert-butyl-4-methylphenol)
Deenax	2,6,Di-tert-butyl-p-cresol
Ionol	2,6-Di-tert-butyl-p-cresol
1-Naphthol	1-Naphthol
2-Naphthol	2-Naphthol
Naugawhite	Alkylated phenol
Nevastain A	Not disclosed
Nevastain B	Not disclosed
Nonyl phenol	Nonyl phenol
p-Phenyl phenol	p-Phenyl phenol
Polygard	Tris (nonylated phenyl) phosphite
Santovar A	2,5-Di-tert-amyl-hydroquinone
Santovar O	2,5-Di-tert-butyl-hydroquinone
Santowhite Crystals	4,4'-Thio-bis (6-tert-butyl-2-methylphenol)
Santowhite MK	Reaction product of 6-tert-butyl-m-cresol and SCl_2
Santowhite Powder	4,4'-Butylidene-bis (3-methyl-6-tert-butylphenol)
Solux	N-p-Hydroxyphenyl-morpholine
Stabilite white powder	Not disclosed
Styphen 1	Styrenated phenol
Wingstay S	Styrenated phenol
Wingstay T	A hindered phenol

Antioxidants

Amine	Trade name
N-Phenyl-1- naphthylamine	Neozone A (a)
N-Phenyl-2-naphthylamine	Neozone D (a)
p-(p-Tolyl-sulfonylamido)-diphenylamine	Aranox (b)
Nonylated diphenylamines	Polylite (b)
Octylated diphenylamines	Age Rite Stalite (c)
Octylated diphenylamines	Age Rite Stalite S (c)
Octylated diphenylamines	Octamine (b)
4,4'-Dimethoxy-diphenylamine	25% of Thermoflex A (a)
4-Isopropoxy-diphenylamine	Age Rite Iso (c)
4-Isopropylamino-diphenylamine	Nonox ZA (d)
N,N'-Di-isopropyl-p-phenylenediamine	Tenamene 5 (e)
N,N'-Di-sec-butyl-p-phenylenediamine	Tenamene 2 (e)
N,N'-Bis(1,4-dimethylpentyl)-p-phenylenediamine	Eastozone 33 (e)
N,N'-Bis(1-ethyl-3-methylpentyl)-p-phenylenediamine	UOP 88 (f)

Stabilizers

Dibutyltin dilaurate
Dioctyltin dilaurate
Butyltin trichloride
Dimethyltin dichloride
Diphenyltin dichloride

Hexabutylditin

Tributyltin laurate
Dibutyltin bis-(2-ethylhexylthioglycollate)

Distearyl thiodipropionate
Dilauryl thiodipropionate
4,4'-Thiobis(6-tert-butyl-m-cresol)
1,1'-Thiobis(2-naphthol)
Triphenyl phosphite
Triethyl phosphite
Tri-p-tolyl phosphite
Tris(dinonyl phenyl)-phosphite
2,2'-Thiobis(6-tert-butyl-p-cresol)
Tri-isopropyl phosphite

Some Ultraviolet Absorbers for Use in Plastic Materials.

	Chemical formula	Trade Name	Manufacturer
1.	2-hydroxy-4-methoxy-benzophenone	Uvinul M 40 Uvistat 24 Cyasorb UV 9	General Aniline Co. Ward & Blenkinsop Cyanamid
2.	2,4-dihydroxy-benzophenone	Uvistat 12 Uvinul 400	Ward & Blenkinsop General Aniline Co.
3.	2-hydroxy-4-methoxy-4-methyl-benzophenone	Uvistat 2211	Ward & Blenkinsop
4.	2,4,5-trihydroxy butyrophenone	Inhibitor THBP	Eastman
5.	4-dodecyloxy-2-hydroxy benzophenone	Inhibitor DOBP	Eastman
6.	2-hydroxy-4-n-octoxybenzophenone	Cyasorb UV 531	Cyanamid
7.	2,2'dihydroxy-4-methoxy benzephenone	Cyasorb UV 24	Cyanamid
8.	2,2'dihydroxy-4,4' dimethoxy benzophenone	Uvinul D 49	General Aniline Co.
9.	p-tert-butylphenylsalicilate		
10.	resorcinol mono benzoate	Inhibitor RMB	Eastman
11.	hydroxyphenylbenzotriazole	Tinuvin P	Geigy
12.	7-diethylamino-4-methyl coumarin		Ward & Blenkinsop

Peroxide Initiators

Group 1

Benzoyl peroxide[a]

Bis(2,4-dichlorobenzoyl)peroxide[b]

Succinic acid peroxide[b]

Lauroyl peroxide[b]

Acetyl peroxide[c]

Bis(1-hydroxylheptyl)peroxide[b]

Peroxyacetic acid

Peroxybenzoic acid

Group 2

Methyl ethyl ketone peroxide[b]

Phenylcyclohexane hydroperoxide[d]

Di-tert-butyl perphthalate[b]

Group 3

tert-Butyl peracetate[b]

tert-Butyl perbenzoate[b]

Group 4

p-Menthane hydroperoxide[d]

Cumene hydroperoxide[d]

tert-Butylisopropylphenylhydroperoxide[d]

Pinane hydroperoxide[d]

Diisopropylphenylhydroperoxides

tert-Butyl hydroperoxide[b]

Hydrogen peroxide

Group 5

Ascaridole[f]

Group 6

Di-tert-butylphenyl oxide[b]

1-Phenylmentane-tert-butyl-peroxide

Accelerator	Trade name
Tetramethylthiuram monosulfide	Unads(c)
Tetrabutylthiuram monosulfide	Pentex(b)
Tetramethylthiuram disulfide	Methyl Tuads(c)
Tetraethylthiuram disulfide	Ethyl Tuads(c)
Dipentamethylenethiuram tetrasulfide	Tetrone A(a)
Cyclic thiuram	Conac T(a)
Piperidinium pentamethylene-dithiocarbamate	Accelerator 552(a)
Zinc dimethyldithiocarbamate	Methyl Zimate(c)
Zinc diethyldithiocarbamate	Ethyl Zimate(c)
Zinc dibutyldithiocarbamate	Butyl Zimate(c)
Copper dimethyldithiocarbamate	Cumate(c)
Bismuth dimethyldithiocarbamate	Bismate(c)
Selenium dimethyldithiocarbamate	Methyl Selenac(c)
Tellurium diethyldithiocarbamate	Tellurac(c)
Cadmium diethyldithiocarbamate	Cadmate(c)
Lead diethyldithiocarbamate	Ethyl Ledate(c)
2-Benzothiazyl-N,N-diethylthiocarbamyl sulfide	Ethylac(q)
2-Mercaptobenzothiazole	MBT(a)
Benzothiazyl disulfide	MBTS(a)
Zinc benzothiazyl sulfide	Zetax(c)
2-Mercaptothiazoline	2-MT(m)
N-tert-Butyl-2-benzothiazole sulfenamide	Santocure NS(h)
N,N-Diispropyl-2-benzothiazole sulfenamide	DIBS(m)
N-Cyclohexyl-2-benzothiazole sulfenamide	Santocure(h)
N-Oxydiethylene-2-benzothiazole sulfenamide	Amax(c)
2-(2,6-Dimethyl-4-morpholino-thio) benzothiazole	Santocure 76(h)
N,N-Dimethylcyclohexylamine salt of dibutyldithiocarbamic acid	RZ-50A(h)
1,1-Methylene-dipiperidine-carbon disulfide reaction product	R-2 Crystals(h)

Accelerator or antioxidant	Reputed composition
Group A	
Vulcafor DOTG	di-o-tolyl guanidine
Vulcafor DPG	diphenyl guanidine
Vulcafor TPG	triphenyl guanidine
Vulcafor TC	thiocarbanilide
Vulcafor MBT	mercaptobenzthiazole
Vulcafor MBTS	dibenzthiazolyl 2-disulphide
Vulcafor TMT	tetramethylthiuram disulphide
Vulcafor MS	tetramethylthiuram monosulphide
Vulcafor TET	tetraethylthiuram disulphide
Santocure	2-benzthiazolyl N'-cyclohexyl sulphenamide
Neozone A (PAN)	Phenyl α-naphthylamine
Neozone D(PBN)	phenyl β-naphthylamine
Agerite White	sym-di-β-naphthyl p-phenylene diamine
MTD	m-toluylene diamine
DPPD	sym-diphenyl-p-phenylene diamine
Group B	
ZMC	zinc dimethyldithiocarbamate
Vulcafor ZDC	zinc diethyldithiocarbamate
Vulcafor ZNBC	zinc di-n-butyldithiocarbamate
Vulcafor MA	formaldehyde-aniline condensation product
Vulcafor RN	acetaldehyde-aniline condensation product
Nonox NS	phenol-adehyde-ketone
Nonox S	aldol-naphthylamine condensation product
Flectol H	polymerized trimethyl dihydroquinoline
Perflectol	(found Flectol H and DPPD)
Neozone C	(found m-toluylene diamine (MTD) and phenyl α-naphthylamine)
Neozone HF	(found phenyl β-naphthylamine and sym-di-phenyl-p-phenylene diamine (DPPD))
Ureka White	(found MBT and guanidine derivative)
Vulcafor DAU	(found TED and MBTS)
Vulcafor DAW	(found MBT and guanidine derivative)
Vulcafor DHC	(found MBT and ZDC)
Vulcafor F	(found MBTS and guanidine derivative)
Vulcafor FN	(found MBTS and guanidine derivative)

Monomeric plasticizers employed in general purpose PVC formulations
Campbell et al[478]

Plasticizer	Characteristics
Diethyl phthalate	Very good softening properties but now little used because it is somewhat volatile.
Di-n-butyl phthalate	Good softening properties but rather volatile and water soluble.
'Dialphanol'* phthalate (*synthetic C_7-C_9 alcohols)	A general purpose plasticizer with good low temperature properties.
Di-2-ethyl hexyl phthalate	An excellent general purpose plasticizer generally referred to as DOP.
Di-iso-octyl phthalate (DIOP)	Very similar in properties to DOP, although volatile loss is slightly better and heat stability and water extraction a little inferior to DOP.
Dicapryl phthalate	Similar in properties to DIOP but more resistant to hydrolysis.
Di-iso-decylphthalate	Another widely used plasticizer. Although not as efficient as DOP it has excellent electrical properties and volatile characteristics.
Butyl benzyl phthalate	Used almost exclusively in floor tile compositions. It is a fast fusing volatile plasticizer but has excellent stain resistance.
Tritolyl phosphate	Often used to impart flame and fungus resistance to PVC compounds
Trixylyl phosphate	The properties are similar to tritolyl phosphate but has a markedly less softening action.
Tri-octyl phosphate	Good low temperature properties but is rather difficult to process.
Di-butyl adipate	Good low temperature properties but somewhat volatile.
Di-2-ethylhexyladipate	A widely used plasticizer with good low temperature properties and plasticizing efficiency, although it exhibits poor volatility characteristics in P.V.C.
Di-iso octyl azelate	A plasticizer with marginally better low temperature properties than the adipates coupled with low volatility and better permanence.
Di-2-ethylhexyl azelate	Similar in properties to the iso-octyl isomer.
Di-iso octyl sebacate	A plasticizer with excellent low temperature properties and volatility characteristics but rather costly.

Poly(Vinyl Chloride) Compound Formulations

All ingredients were used as received from suppliers and are given in parts by weight.

Ingredient	A	B	C
Poly(vinyl chloride) resin	100	100	100
Kodaflex DOP	40	-	60
Plastolein 9058	20	-	-
Morflex 510	-	60	-
Paraphlex G-62	-	5	-
Flexol EPS	5	-	-
Ferro 909	-	-	1
Liquid barium-cadmium-zinc stabilizer	2.5	2.5	2.5
Stearic acid	0.3	0.3	0.3
Calcium carbonate	10	10	10
Titanium dioxide	2	2	2

APPENDIX B

PARTIAL TOXICOLOGY LITERATURE ABSTRACTS

As part of the investigation of hazards associated with contaminants from plastic pipe, several preliminary literature surveys were conducted. The initial emphasis was on chemicals which do not yet have formal recognition as chronic or carcinogenic substances. We examined the four major solvents, the phthlate esters and n,n nitrosodiphenylamine. Here we present abstracts prepared by Thomas Reid Associates of those articles which could be easily obtained -- roughly one third of the total bibleography for these compounds. None of those articles reviewed was excluded from this list.

In reviewing these abstracts, note the difficulty that researchers have in obtaining consistant results and in establishing the proper conditions to elucidate the effects of long term exposure to low concentrations. It is often only after many years does a true pattern of chronic toxicity emerge.

* * * * *

Thomas, John A.; Darby, Thomas D.; Wallin, Richard F.; Garvin, Paul J.; Martis, Leo
A review of the biological effects of di-(2-ethylhexyl)phthalate
Journal: Toxicol. Appl. Pharmacol. 45:1-27

COMPOUND: DEHP

TYPE OF TEST	EXPERIMENTAL SUBJECT	DOSE	FINDINGS
intraperitoneal injection	mouse	LD_{50} of 14.2 g/kg	Acutely toxic
	mouse	LD_5 of 20.0 g/kg	Acutely toxic
	rat	50 ml/mg	Acutely toxic
oral administration	rat	26 g/kg	Acutely toxic
intravenous injection	rat	13 ml/kg	Acutely toxic
oral administration	rabbit	34 g/kg	Acutely toxic
intraperitoneal injection	rabbit	31 g/kg	Acutely toxic
dermal application	rabbit	20 ml/kg	Acutely toxic
dermal application	guinea pig	10 g/kg	Acutely toxic
bioassay	aquatic invertebrates	LC_{50}: 32 mg/l	Acutely toxic
4-hr exposure to continuous mist inhalation	rats	not reported	Death
single oral adm.	dogs	2 g/kg	No toxic manifestations
single oral adm.	adult male	10 g	Mild gastric disturbance, moderate catharsis.
intradermal injection	rabbits	not reported	Mild skin irritation
intradermal or intramuscular injection in PVC	rats, rabbits	not reported	No inflammatory resp.
diet for approx.	rats, guinea	60 mg/kg/day	No effect

1 year	pig, dog		
diet for 13 weeks	rats	200 mg/kg/day	Growth retardation, testicular atrophy
diet for 104 days	rats	60-200 mg/kg/day	Growth retardation, increased liver and kidney weights; no significant histopath. findings
intravenous admin. twice weekly for 63 days	rats	3.7 mg/kg	No measurable effects
general: several types	rats	various	Chronic LD_{50} values several times the acute LD_{50} values.
association of plasma and platelets with DEHP	human and dog blood	not reported	Varied
diet	rats	600 mg/kg	Lung irritations and abnormalities
single injection IV	dogs	1000 mg/kg	Death
intravenous injection 6 day/wk for 4 weeks	dogs	up to 100 mg/kg	Increases in lung and liver weights; pneumonia
5-day tissue culture	human fetal lung cells	60 mg/ml in Polysorbate 80	No cellular damage
intraperitoneal injection at 1, 5, 10 days	rats	5 ml/kg	Alterations in liver enzyme activity
oral admin, daily for 21 days	rats	2 g/kg	Liver enzyme alterations and inhibition
weekly transfusion for 1 year with blood stored in PVC bags	Rhesus monkey	--	Pathophysiologic changes in liver function
single intraperitoneal injection	mice	500 mg/kg emulsified	Significant reduction in sleeping time
single intraperitoneal injection	mice, rats	250, 500 mg/kg in acacia emulsion	Significant increase in sleeping time

single intra-peritoneal injection	mice	300 mg/kg in mouse emulsion	30-50% increase in sleeping time
oral administration daily for 5 days	rats	500 mg/kg	36% reduction in sleeping time
single intravenous administration	male rats	600 mg/kg in acacia emulsion	40% increase in sleeping time
oral admin. for 1 year	dogs	0.09 ml/kg/day	Liver abnormalities
oral admin. for 1 year	guinea pigs	not reported	No liver abnormalities
oral admin. for 2 years	rats	0.4 and o.13%	Liver abnormalities
tissue culture	human embryo cells	0.05 mg/ml	Cytotoxic
90-day feeding	rats	1.5%, 3%	Tubular atrophy, testicular degeneration
intraperitoneal injection	rats	5 ml/kg	Enzyme activity increase in gonads; tubular and testicular degeneration.
diet for 14 mo.	ferrets	1% w/w	Cell changes in testes; sterility
oral admin.	dogs	none reported	No adverse fetal effects
oral admin.	rats	none reported	Aborted fetuses
intraperitoneal injection during pregnancy	rats	5 and 10 ml/kg	No interference with fertility (implantation)
oral admin.	rats	1.7 g/kg/day	Embryonic and fetal toxicity
intravenous injection during pregnancy	rats	1 and 3.7 mg/kg of 185 ug DEHP/ml of rat plasma extract of PVC	No evidence of teratogenics or embryotoxic effects
dominant lethal assay test	mice	none reported	Aborted fetuses and embryos
tissue culture	mouse fibroblasts; 10-day chick embryo	none reported	No cytotoxic effects

tissue culture	human diploid cell strain WI-38	none reported	Inhibition of growth
tissue culture	human diploid fibroblasts	1.56 mM	Inhibition of growth

ARTICLE: 19 - REVIEW ARTICLE

COMPOUND: phthalate esters - DEHP

TYPE OF TEST	EXPERIMENTAL SUBJECT	DOSE	FINDINGS
(49) storage in PVC container	aqueous soln.	6-24 hours	Not agitated - low levels of DEHP (0.070 to 0.139 mg/ml); agitated - markedly increased levels (.526 to 1.869 mg/l); additional DEHP - colloidal particulates.
(25)			intestinal enzymes capable hydrolyzing various phthalate diesters to the respective monoester and alcohol.
(60) ^{14}C-DEHP radiography of IV injected plasma	mice		rapid accumulation in the liver and kidney, with subsequent high concentrations in the urine, bile and intestinal contents.
(57) IV injection of four different forms of ^{14}C-DEHP	mice	sonicated in polysorbate 80-saline	biphasic-disappearance -- half-lives of first phase 4.2-5.9 minutes; half-lives of second phase 31-263i minutes.
		diluted in plasma prior to injection	accumulation and disappearance in liver, lung and spleen influenced by form in which ^{14}C-DEHP was administered
		dissolved in alcohol and stirred into plasma	

			extraction of DEHP from PVC strips stored in plasma	
(50)	IV injection	rat		7-day LD_{50}=238.5 mg/kg in a vehicle of 13.3% polysorbate-80 in normal saline (LD_{50} of solvent=11.1 ml/kg)
(29)		chick embryos		DEHP highly toxic but not teratogenic to 3-day-old chick embryos; degeneration of extra-embryonic blood vessels.
(54)	(dibutyl phthalate)	yeast culture	10 ug/ml to 100 ug/ml	10 ug/ml markedly reduced 48 hr survival of yeast cells; 100 ug/ml had no pronounced mutagenic effect
(16)	analysis of pressed heart extract and residue tissue from human infants who received umbilical catheterization and/or blood products			mean of $1.27^{+}0.42$ ug/g in residue tissue of plastics exposed group and $0.66^{+}.22$ug/g in pressed extract; in controls, less than $0.07^{+}0.03$ and less than $0.07^{+}0.04$ respectively.
(44)	determine DEHD concentration	human placenta		$0.06^{+}0.02$ ppm in placenta of women who gave birth to a normal baby . (comparable to above value, 0.07 ug/g, from control infants in study above).
(11)	IV injection	pregnant rats	185 ug/ml conc. 20 mg/kg on gestation days 6 and 15, as well as same volume of diluted sample containing 50 ug DEHP/ml	No effect upon growth rates of dams, litter size pups (size, weight or viability) nor upon incidence of gross external, skeletal or visceral defects.
(59)	IV injection mono-2-ethyl-hexyl phthalate	pregnant rabbits	1.14, 5.69, 11.38 mg/kg daily for 13 days starting 6th day of	No significant drug effect upon number of size of litters, sex ratio, fetal weight, fetal crown-rump, or transumbilical measure-

			gestation	ments, corpora lutea, or resorptions; dose-related decrease in percentage of live fetuses, dose-related increase in maternal mort.
(8,9)	gastric intubation	male rats	2 g/kg daily	More rapid excretion of ^{65}Zn; 30% loss of testicular weight after 4 days; significant decrease in Zn concentration in testes; increase in calcium excretion
(37)	injection	male rats	1.25 ml/kg/day for 5 days	Significantly lower concentration of testosterone in testicular venous blood.
	IV injection		100 I.U. human chorionic gonadotropin	Testosterone concentration less in DEHP-pre-treated rats.
(51)	i.p. injection	adult male and prepuberal female rats	5 ml DEHP/kg on days 1, 5 10	Significant decrease in succinic dehydrogenase activity and adenosine triphosphate; increase in B-glucoronidase activity in ovaries and testes; testes abnormalities.
(28,52)	sleeping time	rats and mice	treated with DEHP 18 hrs previous to administration of tranquilizer; amount of doses not noted	Pentobarbital sleeping time was increased in male and female rats, methagualone sleeping time was increased in male and female mice.
(35)	phthalate esters: in vitro	intact and sonicated rat liver mitochrondria; purified beef liver glutamate dehydrogenase		"Phthalate esters are electron and energy transport inhibitors, but not uncouplers". Phthalate esters inhibited NADH oxidation by sonicated mitochondira.
(58)	phthalate diesters, monoesters, postassium phthalate, 2-ethyl hexanol: in vitro	rat liver mitochondria		N-propyl phthale the most potent member of the series in inhibiting State-3 respiration. DEHP showed no effect, mono-2-ethyl-hexyl phthalate had the strongest inhibitory effect of all phthalates tested.

(36) phthalate esters: in vitro	yeast, pig heart rabbit muscle		Yeast, glucose-6-phosphate and pig heart malate dehydrogenase were found to be inhibited by phthalate esters. As the length of the chain increased, so did the strength of inhibition.
(18) phthalate esters: in vitro	rat liver mitochondria		Di-n-butyl phthalate uncouples mitochondrial oxidative phosphorylation; other phthalates strongly inhibited respiratory control and ADP:O ratio.
(26) DEHP:diet	ferrets and rats	1% w/w of DEHP for 14 months	Some enzyme activity inhibited, increase in liver weight.
(55) DEHP: intraperitoneal injection	rats	5 ml/kg on days 1,5 and 10; animals sacrificed on day 22	Significant increase in liver weight; decrease in total, free and esterified cholesterol; inhibition of some enzymes.
(5,6) DEHP: diet	rats	0.5 or 1.0% w/w for 10 or 18 days	Consistent and significant increase in liver weight; inhibition of enzymes which was related to duration of DEHP consumption.
(45) DEHP: diet	rats and mice	rats: 0.5, 2.0, 4.0% for 1 or 4 weeks. mice: 2.0 to 4.0% for 1 or 4 weeks	Relative hepatomegaly, decrease in concentration of serum cholesterol and triglycerides; some enzyme activity increased.
(7) phthalates: diet	rats	2.5 mmole/100 gm for 21 days; 1% DEHP, 0.5% dimethyl phthalate, 0.7% di-n-butyl phthalate	DEHP produced the greatest increase in liver weight, decrease in serum cholesterol.
(39,40) DEHP: diet	rats, mice, guinea pigs		Increased liver weight in rats and mice.
(28) phalates: survey	environment		"Instances were noted of presence of phthalate ester contamination of food, water (rivers, lakes and ocean), and air (restricted locations); also of the biological concentration

				(magnification) of phthalate levels of aquatic organisms."
(31)	^{14}C-DEHP aquatic environment	rainbow trout	0.5 ppm for 24 hours	Trout were found to concentrate DEHP and excrete much of it via the bile; concentration of radioactivity at more than 200 times that of the water in the tank - 1% of that was unchanged DEHP and 72% was MEHP.
(48)	phthalate esters: biodegradation of phthalic acid esters (PAE) by Mississippi river water and by activated sludge			"Mixed microbial populations in the environment will degrade PAE esters."
(2)	DEHP: perfusion	isolated rat heart	100 ul/l (2.5×10^{-4}M)	Decreases in spontaneous heart rate, coronary flow rate and isometric systolic tension, while diastolic tension was increased.

COMPOUND: cyclohexanone

TYPE OF TEST	EXPERIMENTAL SUBJECT	DOSE	FINDINGS
acute toxicity by oral or intraperitoneal injection.	mice, rats, rabbits, guinea pigs	Reported are LD_{50}'s 0.93-2.11 g/kg	Those animals dying did so within 24 hrs. They showed symptoms of acute poisoning, CNS depression and respiratory failure.
inhalation toxicity	male mice	concentration in air: 10-20 mg/l	Mean time to death was 100 min.; lungs of dead animals were acutely congested with hemorrhage of the lung tissue.
inhibition of cell (fibroblast) growth	mouse fibroblast	determination of concentration to reduce growth by 50% (IC50)	0.0195 moles/liter of cyclohexanone was the IC50.
cumulative toxicity	male ICR mice	daily (5 days/week) injection of cyclohexanone	Toxicity increased with time, indicating that toxicity was cumulative. (After 10 weeks, the LD_{50} was 1/10 of the acute

			LD_{50})
opthalmic irritation	rabbits	5-40% in cottonseed oil	Irritation was dose-dependent.

QUOTE: "Because of the apparent cumulative toxicity exhibited by the compound insure there is no residue in the device.)"

Couri, Daniel; Abdel-Rahman, Mohamed S.; Hetland, L. B.
Biotransformation of n-hexane and methyl n-butyl ketone in guinea pigs and mice
Journal of the American Industrial Hygene Association 39:295-300

COMPOUND: n-hexane, MBK, MEK

TYPE OF TEST: intraperitoneal injection; exposure to solvent vapors

EXPERIMENTAL SUBJECT: guinea pigs and mice

DOSE: guinea pigs: 132 mg undiluted n-hexane (animals weighed 210±20g)
40/120 mg MBK/MEK.
mice: 15 mg mice in one m^3 chamber. 150 ppm MBK, 150/1000 ppm MBK/MEK or 1000 ppm MEK vapors continuously for one week.

FINDINGS: MBK/MEK (3:1) vapors caused an increased severity and shortened onset of neurotoxicity compared to MBK alone. Sleep time diminished suggesting that exposure to ccombined solvent vapors caused an alteration in liver biotransformation activity.

QUOTE: "The in vivo and in vitro biotransformation of MBK and n-hexanes as a common metabolite (2-hexanol) suggests that the neurotoxication of these solvents may be metabolite related."

Jacobson, M. S.; Parkman, R.; Button, L. N.; Jaeger, R. J.; Kevy, S. V.
Toxicity of human serum stored in flexible polyvinylchloride containers on human fibroblast cell cultures. Effect of bis(2-ethylhexyl phthalate)
Journal: Res. Commun. Chem. Pathol. Pharmacol. 9:315-323

COMPOUND: DEHP

TYPE OF TEST: tissue culture

EXPERIMENTAL SUBJECT: human diploid fibroblasts

DOSE: 0.15mMol DEHP from 21 day old blood out of PVC containers and stored at 4°C. 0.70mMol DEHP found in platelet concentrates stored 48 hrs at 22 °C.

FINDINGS: Tissue culture medium concentration of DEHP of 0.10mMol causes a 20% inhibition of cell growth. A concentration of DEHP of 0.18mMol caused 50% inhibition of fibroblast growth. As the concentration of DEHP is increased there is a greater degree of inhibition of human diploid fibroblast growth.

QUOTE: "The in vitro toxicity of physiologically solubilized DEHP raises concern about its possible in vivo toxicity in these multiply transfused patients or in patients receiving older whole blood."

Stula, E. F.; Krauss, W. C.
Embryotoxicity in rats and rabbits from cutaneous application of amide-type solvents and substituted ureas
Journal: Toxicol. Appl. Pharmacol. 41:35-55

COMPOUND: DMF (among others)

TYPE OF TEST: epidermal application

EXPERIMENTAL SUBJECT: rabbits and rats (pregnant)

DOSE: 600-2400 mg/kg. 1/28 of ALD (approx. lethal dose)

FINDINGS: DMF caused significant embryomortality in rats only at a dose that resulted in maternal mortality. No embryonic effects found in rabbits given a total dose of DMF 1800mg/kg equal to 1/2 of the skin ALD during days 8-16 of gestation.

QUOTE: "Marked embryomortality was found with MMF and TMU; moderate with DMAC, TMTU, and TDOT; and slight with F, DBF, MMAC, and DMF."

Schulz, Carl O.; Rubin, Robert J.; Hutchins, Grover M.
Acute lung toxicity and sudden death in rats following the intravenous administration of the plasticizer, di(2-ethylhexyl) phthalate, solubilized with Tween surfactants
Journal: Toxicol. Appl. Pharmacol. 33:514-525

COMPOUND: DEHP

TYPE OF TEST: intravenous

EXPERIMENTAL SUBJECT: rat

DOSE: up to 300 mg/kg in aqueous solutions

FINDINGS: accute lung toxicity; sudden death; dose-dependent lethality.

QUOTE: "Another area which requires further investigation is the possible biological effect of chronic oral ingestion of phthalate ester plasticizers. It is important to determine whether natural surfactants such as bile salts in the gut have the capability to form solubilized micelles of DEHP which might then enter the bloodstream and give rise to subacute alterations in the lungs or other tissues."

Lake, Brian G.; Brantom, Paul G.; Gangolli, Sharat D.; Butterworth, Kenneth R.; Grasso, Paul
Studies on the effects of orally administered bis-(2-ethylhexyl) phthalate in the ferret
Journal: Toxicology 6:341-356

COMPOUND: DEHP

TYPE OF TEST: target-organ study; metabolic study; diet

EXPERIMENTAL SUBJECT: ferret

DOSE: 1% diet, 14 months

FINDINGS: loss of body weight, liver enlargement and associated changes; hepatotoxic; testicle abnormality.

QUOTE: "The observed similarities in the hepatic and testicular effects of the metabolism ofDEHP between a rodent and a non-rodent species highlight the need for an assessment of phthalate esters in terms of human exposure."

Lake, B. G.; Gangolli, S. D.; Grasso, P.; Lloyd, A. G.
Hepatic effects of orally administered bis(2-ethylhexyl) phthalate in the rat
Journal: Toxicol. Appl. Pharmacol. 32:355-367

COMPOUND: DEHP

TYPE OF TEST: hepatic effects of oraly administered DEHP

EXPERIMENTAL ANIMAL: rat

DOSE: 2000 mg/kg for 21 days

FINDINGS: progressive liver enlargement and associated changes

QUOTE: "The results indicate that the partial hydrolysis of DEHP to the monoester (MEHP) is the degradative step which determines the hepatic changes produced by DEHP. It is arguable that our finding in the rat obtained at a dose level of 2000 mg/kg may not be relevant in the context of the toxicological assessment of DEHP in terms of human exposure. However, in a 90 day feeding study of DEHP in rats conducted in our laboratories, liver enlargement was observed at all the dose levels investigated (100-1000 mg/kg/day)."

Jones, Adelaide E.; Kahn, Raymond H.; Groves, John T.; Napier, Edward A., Jr.
Phthalate ester toxicity in human cell cultures
Journal: Toxicol. Appl. Pharmacol. 31:283-289

COMPOUND: principally DEHP and BGBP; also di-n-butyl phthalate, di-iso-butyl phthalate, dimethoxyethyl phthalate, di-n-octyl phthalate; two non-phthalide PVC-leachable compounds, di-2-ethylhexyl adipate and 2,6-di-tert-butyl cresol

TYPE OF TEST: cell culture - in vitro (Eagles basal medium with 10% calf serum)

EXPERIMENTAL SUBJECT: human cells (human diploid cell strain WI-38)

DOSE: DEHP 51-160uM; BGBP 7-14uM.

FINDINGS: decreased cell protein, decreased cell density; DEHP effects not reversible; non-replicating cells less affected than replicating ones; thalate esters and non-thalide leachable compounds toxic at low levels.

QUOTE: "Although there have been no observations of clinical problems attributable to the use of these compounds, there is experimental evidence of subtle toxicity due to many phthalate esters found in PVC-containing plastics,

as well as the possibility of tissue accumulation of DEHP."

Gray, T. J. B.; Butterworth, K. R.; Gaunt, I. F.; Grasso, P.; Gangolli, S. D.
Short-term toxicity study of di-(2-ethylhexyl) phthalate in rats
Journal: Food Cosmet. Toxicol. 15:389-399
COMPOUND: DEHP

TYPE OF TEST: diet

EXPERIMENTAL SUBJECT: rats - male and female

DOSE: 0-2% diet for 17 weeks

FINDINGS: 1% and 2%: reduced rate of body-weight-gain and food intake; decreased packed-cell volume; reduced hemoglobin concentration in males; reduced renal concentrating and diluting ability in females receiving 2%; relative weights or organs to body weight higher than controls; decreased relative testis weight, seminiferous tubular atrophy, cessation of spermatogenesis. 02%: decreased spermatogenesis. All treatment levels: dose-related castration cells in the pituitary.

QUOTE: "In view of the testicular changes and the increase in liver weight at all treatment levels, it was not possible to establish a no-untoward-effect level for DEHP in this study."

"Earlier views on the safety-in-use of DEHP as a plasticizer in packaging for direct food contact have been based on the collected findings of studies reported by Carpenter et. al. (1953) and Harris et. al. (1956). These established that at 0.1% in the diet of rats no untoward effects attributable to the feeding of DEHP were apparent after 2 yr. This corresponds to an acceptable dietary intake of the order of 30 mg/day for a 60 kg. adult, after an application of the traditional 100-fold safety factor. The present investigations demonstrate that in rats fed 0.2% DEHP in the diet for periods of up to 17 weeks, effects on the liver and testes were discernible. It must be considered unfortunate that no definitive information is available on the extent to which this plasticizer migrates from packaging into food under various storage conditions. Consequently, the significance of these findings in relation to human exposure remains to be determined. In the interim, continuing reliance must be placed on the work of Harris et. al. (1956) as the basis for assessing safe human intakes."

Mayer, Foster L., Jr.; Sanders, Herman O.
Toxicology of phthalic acid esters in aquatic organisms 73 3:153-157
Journal: Environ, Health Perspect. Publ. 73 3:153-157

COMPOUND: phthalic acid esters: di-n-butyl phthalate and di-2-ethylhethy phthalate (DEHP)

TYPE OF TEST: static and flow-through bioassay

EXPERIMENTAL SUBJECT: aquatic organisms: water flea, scud, midge, mayfly, fathead minnow, gluegill, channel catfish, rainbow trout, scud, crayfish, zebrafish, guppy.

DOSE: toxicity: 0-10 mg/l; accumulation and excretion: 0.08-1.9 uM/l; reproduction: 3-30 ug/l (di-n-butylphthalate -- waterfleas); 50-100 ug/l (di-2-ethylhexyl phthalate -- zebrafish, guppies).

FINDINGS: Toxicity: relatively low. Accumulation and Excretion: initial rapid uptake to several hundred times water concentration, less rapid elimination in fresh water.

QUOTE: "The concentrations of phthalic acid esters presently found in waters of the United States are, in some cases, detrimental to aquatic invertebrates in view of laboratory results."

Easterling, Ronald, E.; Johnson, Elvin; Napier, E. A., Jr.
Plasma extraction of plasticizers from medical grade polyvinylchloride tubing
Journal: Proc. Soc. Exp. biol. Med. 147:572-574

COMPOUND: PVC, DEHP, DEHA

TYPE OF TEST: recirculation in "medical grade" PVC tubing, samples from five sources.

EXPERIMENTAL SUBJECT: human blood

DOSE: 0-6 hours

FINDINGS: concentration of DEHP as high as 35.9 ug/ml; presence of DEHA in one sample and DTBC in one sample.

QUOTE: "Since extraction of DEHP was nearly linear in the tubing examined, even higher levels probably would be achieved with longer perfusion at 37°. The observation that DEHA was also found in one specimen, in addition to DEHP, suggests that at least three formulations of PVC tubings were involved. Accordingly, when the toxicology of such materials is in question, observations should be made for each source of the PVC tubing."

Tanaka, Akira; Adachi, Toru; Takahashi, Terue; Yamaha, Tsutomu
Biochemical studies on phthalic esters. 1. Elimination, distribution, and metabolism of di(2-ethylhexyl)phthalate in rats
Journal: Toxicology 4:253-264

COMPOUND: DEHP

TYPE OF TEST: IV and oral dose using carbon 14 tracers

EXPERIMENTAL SUBJECT: rats

DOSE: 500 mg/kg oral; 50 mg/kg IV

FINDINGS: Orally, no significant retention in other organs than GI tract; IV, traced in all organs and adipose tissue; low levels found in brain and

testis using both methods.

QUOTE: "It is clear that repeated administration of DEHP may lead to its accumulation in the body until a steady state is reached between the rates of absorption and elimination."

Rubin, Robert J.; Jaeger, Rudolph J.
Pharmacologic and toxicologic effects of bis(2-ethylhexyl)phthalate (DEHP) and other plasticizers
Journal: Environ. Health Perspect. 3:53-59

COMPOUND: DEHP, BGBP

TYPE OF TEST: intraperitoneal administration

EXPERIMENTAL SUBJECT: male mice and rats

DOSE: 250 mg/kg or 500 mg/kg

FINDINGS: BGBP and DEHP can alter the pharmacologic response to a barbituate; DEHP virtually eliminated all running activity during the subsequent 24 hour period, although animals appeared to be reasonably alert; depending on schedule of administration, DEHP can either depress or stimulate reticuloendothelial function.

QUOTE: " Previous published data on the toxicology of the phthalate esters (including DEHP) have indicated a low order of toxicity. However, the results presented here indicate that under the appropriate conditions, DEHP can be demonstrated to have significant effects on a variety of biological systems."

Altenkirch, H.; Stoltenburg, G.; Wagner, H. M.
Experimental studies on hydrocarbon neuropathies induced by methyl-ethyl-ketone (MEK)
Journal: J. Neurol. 219:159-170

COMPOUND: MEK, MEK/n-hexane

TYPE OF TEST: chronic repeated exposure to air with solvent gas in it.

EXPERIMENTAL SUBJECT: rats

DOSE: 10,000 ppm pure n-hexane; 10,000 ppm MEK/n-hexane in 1:9 ratio; 6,000 ppm pure MEK.

FINDINGS: motor neuropathy of the dying back type with giant swelling of axons in the peripheral and central nervous system from exposure to MEK/n-hexane and n-hexane. With MEK alone, there was no neuropathy under these conditions.

QUOTE: "The findings suggest that commercial solvent mixtures containing MEK/n-hexane should be avoided."

Wahlberg, Jan E.; Boman, Anders
Comparative percutaneous toxicity of ten industrial solvents in the guinea pig
Journal: Scand. J. Work, Environ, Health 5:345-351

COMPOUND: 2-chloroethanol; 1,1,2-trichloroethane; ethyleneglycol monobutylether; CCl_4; DMF; benzene; toluene; 1,1,1-trichloroethane; trichloroethylene; n-hexane.

TYPE OF TEST: epicutaneous administration, intraperitoneal administration.

EXPERIMENTAL SUBJECT: guinea pig

DOSE: percutaneous: 0.5 or 2.0 ml on 3.1cm^2 area (0.7% body area exposed); same amount injected intraperitoneally.

FINDINGS: Subjects exposed to CCl_4, ethyleneglycol monobutylether, DMF died. For the others, no mortalities observed. Reducing the applied volume reduced mortality rate.

Srivastava, S. P.; Agarwal, D. K.; Seth, Prahlad K.
Effect of bis(2-ethylhexyl) phthalate on the acivity of succinic dehydtogenase and adenosine triphosphatase of some vital organs of rat
Journal: Toxicology 7:163-168

COMPOUND: DEHP

TYPE OF TEST: intraperitoneal injections; in vitro conditions.

EXPERIMENTAL SUBJECT: rat

DOSE: 5 ml/kg DEHP (1/10 LD_{50} dose); different concentrations in vitro conditions.

FINDINGS: Succinic dehydrogenase and ATPase activity measured 21 days after 3 intraperitoneal injections of DEHP was decreased in heart, lung and kidney, but unaltered in brain. Only SDH was sensitive to DEHP at different concentrations in vitro conditions.

QUOTE: "Recently, DEHP has gained significance as an environmental pollutant, having been detected in varying quantities in water, fish and aquatic vertebrates as well as in bovine and human tissues. Although DEHP has a low order of oral toxicity, it has been shown to exert teratogenic, mutagenic and cellular toxic effects."

Altenkirch, H.; Stoltenburg-Didinger, G.; Wagner, H. M.
Experimental data on the neurotoxicity of methyl ethyl ketone (MEK)
Journal: Experientia 35:503-504

COMPOUND: MEK, n-hexane

TYPE OF TEST: chronic inhalation

20823080

EXPERIMENTAL SUBJECT: rat

DOSE: 10,000 ppm n-hexane, 99% purity; mixture of 1100 ppm MEK and 8900 ppm n-hexane; 6000 ppm MEK, 99% purity.

FINDINGS: "A severe potentiating effect of MEK on the peripheral and central neurotixicity of n-hexane could be demonstrated in a chronic inhalation study in rats."

QUOTE: "The results of the present study indicate tt the addition of a small amount of MEK to n-hexane (ratio 1:9) manifested markedly enhanced neurotoxicities with a shortened time for occurrence of morphological and clinical signs."

Lee, Hsin-Yi; Kalmus, Gerhard W.; Levin, Martin A.
Effects of phthalate esters (plasticizers) on chick embryos and chick embryonic cells
Journal: Growth 38:301-312

COMPOUND: phthalate esters: DEHP; di(2-butoxyethyl) phthalate; dimethyl phthalate, and di(isodecyl) phthalate.

TYPE OF TEST: in ovo and in vitro and in cultured chick embryonic cells.

EXPERIMENTAL SUBJECT: chick embryos

DOSE: undiluted 0.05 ml/egg Ringers solution; 50 ml of undiluted phthalate ester and 150 ml of Chick's Ringer solution.

FINDINGS: Toxic effects resulting in death of embryos were produced by phthalate esters in undiluted form, but teratogenic effects were not observed in explanted streak stage embryos or hatched chicks. Chick Ringer's solution saturated with phthalate esters caused a distinct growth retardation and produced non-specific malformations, particularly in the CNS.

QUOTE: "It seems probable that the phthalate esters may interfere with absorption of nutrients, and their lethal effects are a secondary consequence of extensive degeneration of extraembryonic blood vessels."

Jacobson, May S.; Kevy, Sherwin V.; Grand, Richard J.
Effects of a plasticizer leached from polyvinyl chloride on the subhuman primate: a consequence of chronic trasfusion therapy
Journal: J. Lab. Clin. Med. 89:1066-1079

COMPOUND: DEHP

TYPE OF TEST: transfusion

EXPERIMENTAL SUBJECT: Rhesus monkey

DOSE: 20.52-108 mg or 6.6 to 33 mg/kg

FINDINGS: DEHP detectable in organ and fat tissue up to 14 months later.

QUOTE: "Although we have not as yet established the metabolic pathway of DEHP in the Rhesus monkey, this finding supports the work of Daniel and Bratt who have demonstrated that DEHP in the rat is metabolized in part to mono-2-ethylhexyl phthalate (MEHP). This metabolite is a potent inhibitor of liver dehydrogenases and theoretically may have greater potential for hepatotoxicity than the parent compound."

Krivanek, Neil D.; McLaughlin, Martha; Fayerweather, William E.
Monomethylformamide levels in human urine after repetitive exposure to dimethylformamide vapor
Journal: J. Occup. Med. 20:179-182

COMPOUND: DMF

TYPE OF TEST: exposure to vapor

EXPERIMENTAL SUBJECT: human male, 20-47 years old, 70-84 kg in weight.

DOSE: (average dose) 8.8_0.7 ppm for 6 hrs/day for five consecutive days.

FINDINGS: Amount of MMF in subject's urine related to duration and level of exposure and physical activity.

QUOTE: "The results of this human study showed that DMF vapor is absorbed by the body and can be correlated wtih urinary MMF after exposure."

Stenchever, Morton A.; Allen, Marjorie A.; Jerominski, Leslie; Petersen, Robert V.
Effects of bis(2-ethylhexyl) phthalate on chromosomes of human leukocytes and human fetal lung cells
Journal: J. Pharm. Sci. 65:1648-1651

COMPOUND: DEHP

TYPE OF TEST: exposure in solution or in culture

EXPERIMENTAL SUBJECT: human blood and human fetal lung cells

DOSE: Blood: 60.0, 0.6, 0.06 ug concentrations at 37^{o} for 4 hrs.
Lung tissue: 6.0 ug/ml for 5 days.

FINDINGS: No increased incidence of chromosomal damage to fetal lung cells or leukocytes.

QUOTE: "Recent publications and reviews confirmed that DEHP probably has a low order of acute toxicity. However, the long-range subtle toxicogenic potential of this agent is becoming of paramount concern."

"While the data are not conclusive and there is incomplete agreement between laboratories, evidence suggests that DEHP and/or its metabolites are toxic at the cellular level, that DEHP interferes with normal reproductive patterns, and that lower molecular weight phthalate esters are teratogenic."

Draft NTP Technical Report on the Carcinogenesis Bioassay of di(2-ethylhexyl)phthalate
Public Health Service, Department of Health and Human Services
15 October 1980

COMPOUND: DEHP

TYPE OF TEST: oral administration

EXPERIMENTAL SUBJECT: rats, mice

DOSE: Acute toxicity test: .08-20 g/kg rats; 1.25-20 g/kg mice (14 days); repeated dose, 5 concentrations of test substance in feed (100,000 ppm) (14 days). Subchronic studies: 1600, 3100, 6300, 12,500, 25,000 ppm (13 weeks). Chronic study: for rats, 6,000 and 12,000 ppm in feed; for mice, 3,000 and 6,000 ppm in feed.

FINDINGS: Rats and mice: dose related decrement in mean body weight; neoplastic nodules of the liver at increased incidences; hepatocellular carcinoma, testicular atrophy.

QUOTE: "Histopathologic examinaion indicated that, under conditions of this bioassay, the administraion of DEMP was associated with an increased incidence of liver tumors in F344 rats."

Oishi, S.; Hiraga, K.
Testicular atrophy induced by phthalic acid esters: effect on testosterone and zinc concentrations
Journal: Toxicol. Appl. Pharmacol. 53:35-41

COMPOUND: DEHP; DBP (di-butyl); DIBP (di-iso-butyl); DOP (di-n-octyl); DMP (di-methyl); DEP; phthalic acid.

TYPE OF TEST: effect of dietary administration of phthalate esters.

EXPERIMENTAL SUBJECT: young male wistar rats

DOSE: 2% by weight phthalate ester

FINDINGS: Testicular atrophy with DEHP, DBP, and DIBP; no testicular atrophy with DOP; zinc concentration decreased with DMP; testosterone level not changed with DEP.

QUOTE: "The degree of testicular injury developed by PAE's may be dependent upon the length and structure of substituted alkyl chains. In the results presented in this report, decrease in zinc concentration was clearly shown in the rats fed diets containing DBP, DIBP, or DEHP."

Seth, Prahlad K.; Srivastava, S. P.; Mushtaq, Mohammad; Agarwal, D. K.; Changra, Satya V.
Effect of di-(2-ethylhexyl)phthalate on rat liver injured by chronic carbon tetrachloride treatment
Journal: Acta Pharmacol. Toxicol. 44:161-167

COMPOUND: DEHP

TYPE OF TEST: synergistic effect of DEHP administered intraperitoneally on rat liver previously injured by CCl_4

EXPERIMENTAL SUBJECT: adult female rats

DOSE: 7.7 mmol/kg subcut. biweekly for 38 days.

FINDINGS: Extensive necrosis of liver cells when both chemicals were present.

Nakamura, Yoshiyuki; Yagi, Yasuoki; Tomita, Isao; Tsuchikawa, Kiyoshi
Teratogenicity of di-(2-ethylhexyl)phthalate in mice
Journal: Toxicol. Lett. 4:113-117

COMPOUND: DEHP

TYPE OF TEST: test for fetal malformations and/or death by oral administration of DEHP

EXPERIMENTAL SUBJECT: mouse strain

DOSE: 0.05-0.1 ml/kg on day 7 of gestation

FINDINGS: 0.05 ml/kg decreased weight of live fetuses; 0.068-0.08 ml/kg resulted in gross and skeletal anomalies. The LD_{50} was 0.60 ml/kg.

QUOTE: "Toxic effects were closely related to the time and dose of administration."

Sugawara, Naoki
Toxic effect of a normal series of phthalate esters on the hatching of shrimp eggs
Journal: Toxicol. Appl. Pharmacol. 30:87-89

COMMAND: phthalate esters: DMP, DEP, DBP, DEHP, DOP.

TYPE OF TEST: to show the toxic order of phthalate esters on hatching of shrip eggs

EXPERIMENTAL SUBJET: brine shrimp eggs

DOSE: incubation of eggs with 10, 20, and 50 ppm solution of PAE's.

FINDINGS: As measured by the number of eggs hatching, the order of increasing

toxicity is DMP, DEP, DBP. 50 ppm of DBP significantly increases egg mortality.

QUOTE: "The toxicity of the phthalates cannot be explained by their solubility alone."

Singh, A. R.; Lawrence, W. H.; Autian, J.
Teratogenicity of phthalate esters in rats
Journal: J. Pharm. Sci. 61:51-55

COMPOUND: DEHP, DMEP, DOP, DMP, DBP, BCBMP, DIBP.

TYPE OF TEST: teratogenic effects of the injection of phthalate esters during gestation (5th, 10th, and 15th days of a 21 day pregnancy)

EXPERIMENTAL SUBJECT: female Sprague-Rawley rats

DOSE: 5 or 10 ml/kg intraperitoneally

FINDINGS: Fetal deaths were observed with DMP, DMEP, DIBP (2-29% of embryos). Most phthalates produced some resorptions. Gross and or skeletal abnormalities were observed with all of the phthalates (up to 100% of the fetuses). Abnormalities included absence of tail or eyes, twised hind legs, elongated and fused ribs and abnormal skull bones.

QUOTE: "The observed incidence of adverse effects was generally dose-related and compound dependent, with the more water-soluble compounds tending to be the most active."

Dunkel, Virginia C.
Collaborative studies on the Salmonella/microsome mutagenicity assay
Journal: J. Assoc. Off. Anal. Chem. 62:874-882

COMPOUND: N-NDPA

TYPE OF TEST: Salmonella test for mutagenesis

EXPERIMENTAL SUBJECT: Salmonella bacteria

DOSE: 0.3-333.3 ug/plate

FINDINGS: N-NDPA gave a negative result; it was not mutagenic when tested by three laboratories with or without activaton.

Archer, Wesley L.; Stevens, Violete L.
Comparison of chlorinated, aliphatic, aromatic, and oxygenated hydrocarbons as solvents
Journal: Ind. Eng. Chem. Prod, Res. Dev. 16:319-325

COMPOUND: Methyl ethyl ketone

TYPE OF TEST: establishment of toxicity criteria for solvents

EXPERIMENTAL SUBJECT: human

DOSE: variable

FINDINGS: At 30 ppm, induced inhalation toxicity.

Cater, Bryan R.; Cook, Melvyn W.; Gangolli, Sharat D.
Zinc metabolism and dibutyl phthalate-induced testicular atrophy in the rat
Journal: Biochem. Soc. Trans. 4:652-653

COMPOUND: DBP

TYPE OF TEST: relationship between zinc metabolism, DBP and testicular atrophy.

EXPERIMENTAL SUBJECT: male Sprague-Dawley rats

DOSE: DBP: 2 g/kg orally in corn oil; ^{65}Zn injected subcutaneously 25 uCi/kg.

FINDINGS: In the presence of DBP there was a significant decrease in Zn in the testes, followed by testicular atrophy. No Zn decrease was noted in the kidney or liver.

United States Environmental Protection Agency
Regulation of New Chemical Substances Pending Development of Information
23 April 1980

COMPOUND: dialkyl phthalates

TYPE OF TEST: bioconcentration potential (physical experiment)

FINDINGS: An increase in alkyl chain length results in an increase in the octanol/water partition coefficient, a simple indicator of the bioconcentration potential of a chemical.

Srivastava, S. P.; Agarwal, D. K.; Mushtaq, M.; Seth, Prahlad K.
Effect of di-(2-ethylhexyl)phthalate (DEHP) on chemical constituents and enzymic activity of rat liver
Journal: Toxicology 11:271-275

COMPOUND: DEHP

TYPE OF TEST: Intraperitoneal injection on 3 days/Examination of liver.

EXPERIMENTAL SUBJECTS: male albino rats

DOSE: 5 ml/kg

FINDINGS: Inhibition of energy, linked reactions, and hepatotoxicity.

Mathew, T.; Karunanithy, R.; Yee, M. H.; Natarajan, P. N.
Hepatotoxicity of dimethylformamide and dimethyl sulfoxide at and above the levels used in some aflatoxin studies
Journal: Lab. Invest. 42:257-262

COMPOUND: dimethyl-formamide

TYPE OF TEST: hepatotoxicity and potential carcinogenicity of DMFA (and dimethylsulfoxide)

EXPERIMENTAL SUBJECT: albino rats

DOSE: single intraperitoneal injection of 0.6 to 1.2 ml/kg

FINDINGS: Liver damage at all dosesof DMF, increasing with dose. Atypical cells a consistent finding after exposure.

QUOTE: "DMFA induced liver cell necrosis probably upsets the normal genetic machinery of the regenerating hepatocytes. These cells then acquire a neoplastic potential that would become manifest at a later time.

Iversen, Olav Bilmar
Tumorgenicity of N-nitroso-diethyl, -dimethyl and -diphenyl-amines in skin painting experiments. A study utilizing the tetrazolium test and skin applications on hairless mice
Journal: Eur. J. Cancer 16:695-698

COMPOUND: N-nitroso-diphenyl-amine (NDPA)

TYPE OF TEST: tumor yield after 20 weekly applications to the skin

EXPERIMENTAL SUBJECT: hairless mice

DOSE: 0.1 ml of a 1% solution

FINDINGS: No skin tumors, but a high proportion of the treated animals developed lung tumors (adenomas).

QUOTE: "The occurrence of lung adenomas is certainly a sign of tumorogenicity and is also usually accepted as a sign of carcinogenicity."

Cardy, Richard H.; Lijinsky, William; Hildegrandt, Paul K.
Neoplastic and nonneoplastic urinary bladder lesions induced in Fischer 344 rats and B6C3F1 hybrid mice by N-nitrosodiphenylamine
Journal: Ecotoxicol. Environ. Saf. 3:26-35

COMPOUND: NDPA

TYPE OF TEST: standard bio-assay by adding NDPA to rat and mouse feed

EXPERIMENTAL SUBJET: Fisher 344 rats; B6C3F mice.

DOSE: rats: 2000-4000 ppm; mice: 5000 to 20,000 ppm (lowered to 1000 to 4000 ppm because of acute toxicity.)

FINDINGS: Urinary bladder cancers were observed in 40% of male rats and 90% of the female rats. In the mice, there were a high incidence of non-neoplastic bladder lesions.

QUOTE: "It is postulated that the bladder tumors in the rats arose not from (direct) exposure to NDPA, but through exposure to a bladder-specific nitrosamine formed by a reaction of an amine probably in the food, with NDPA in the rats stomach."

Li, Gloria C.; Hahn, George M.; Shiu, Esther C.
Cytotoxicity of commonly used solvents at elevated temperatures
Journal: J. Cell. Physiol. 93:331-334

COMPOUND: DMFA, DMSO

TYPE OF TEST: Cell toxicity of solvents when heated to 43°C.

EXPERIMENTAL SUBJECT: Chinese hamster cells; mouse mammary sarcoma cells.

DOSE: DMFA and DMSO: 1-10%

FINDINGS: The presence of the solvents increases the cells' sensitivity to heat.

Lake, Brian G.; Brantom, Paul G.; Gangolli, Sharat D.; Butterworth, Kenneth R.; Grasso, Paul; Lloyd, Alun G.
The hepatic effects of orally administered di-(2-ethylhexyl)phthalate in the ferret
Journal: Biochem. Soc. Trans. 5:310-311

COMPOUNDS: DEHP

TYPE OF TEST: effect on the liver of 1% DEHP in the diet for 14 months

EXPERIMENTAL SUBJECT: adult male albino ferrets

DOSE: 1% DEHP in the diet

FINDINGS: Marked liver enlargement; significant histochemical (enzyme) changes, and cellular ultastruture changes.

QUOTE: "A number of similarities exist between the hepatic effects of DEHP in

the rat and the ferret. Our findings show that DEHP may be considered hepatotoxic in both the rat and the ferret."

Lake, Brian G.; Phillips, John C.; Hodgson, Rosalyn A.; Severn, Brian J. Gangolli, Sharat D.; Lloyd, Alun G.
Studies on the hydrolysis in vitro of phthalate esters by hepatic and intestinal mucosal preparations from various species

COMPOUND: DEHP and 5 other phthalate diesters

TYPE OF TEST: metabolism of DEHP by the liver and intestinal mucosa

EXPERIMENTAL SUBJECT: rat, baboon, ferret

FINDINGS: The liver and intestinal mucosal preparations of all animals hydrolysed the di-esters to mono-esters.

QUOTE: "Orally administered phthalated diesters would probably be absorbed from the small intestine as monoester derivatives."

Sanders H. O.; Mayer, F. L.; Walsh D. F.;
Toxicity residue dynamics, and reproductive effects of phthalate esters in aquatic invertebrates
Journal: Environ. Res. 6:84-90

COMPOUND: Dialkyl phthalates

TYPE OF TEST: toxicity at low concentrations

EXPERIMENTAL SUBJECT: Daphnia

DOSE: variable

FINDINGS: Reproduction was significantly reduced at 20 ppb DBP and at 23 ppb DEHP.

Mayer F. L.; Mehrle, P. M.; Schoettger, R. A.
Collagen metabolism in fish exposed to organic chemicals
EPA-600/3-77-085 NTIS PB 273 500

COMPOUND: DEHP

TYPE OF TEST: survey for developmental anomalies

EXPERIMENTAL SUBJECT: brook trout, fathead minnows, rainbow trout fry

DOSE: variable

FINDINGS: Caused skeletal deformations at 3.7 to 14 ug/L

Mayer, F. L., Jr.; Sanders, H. O.
Toxicity of phthalic acid esters in aquatic organisms
Journal: Environ, Health Perspect. Exp. Iss. 3:153-157

COMPOUND: DEHP and DEP

TYPE OF TEST: bioconcentration potential

EXPERIMENTAL SUBJECT: aquatic invertebrates

FINDINGS: Biocncentration factors of 400-1400 were reported for DBP; higher factors for DEHP.

Metcalf R. L; Booth G. M.; Schuth, c. K.; Hansen D. J.; Lu, P-Y
Uptake and fate of di-2-ethylhexyl phthalate in aquatic organisms and in a model ecosystem.
Journal: Environ. Health Perspect. Exp. Iss. 4: 27-34

COMPOUND: DEHP

TYPE OF TEST: bioconcentration potential

EXPERIMENTAL SUBJECT: aquatic plants and invertebrates in a model ecosystem

FINDINGS: Bioconcentration factors of 21,480 to 107,670 were reported.

Arthur D. Little, Inc.
Risk assessment of priority pollutants: phthalate esters.
EPA Contract No. 68-01-3857, Task 9

COMPOUND: alkyl phthalates

TYPE OF TEST; contamination of water by plasticizers released during processing

FINDINGS: A.D. Little estimated that 1.3 to 2.6% of the total volume of plasticizers used during processing are released in water effluents.

Battelle
Environmental Risk Assessment of Alkyl Phthalates
U.S. EPA Contract No. 68-01-5043

COMPOUND: alkyl phthalates

TYPE OF TEST: contamination of surface water

FINDINGS: Phthalates have been measured at levels of 0.1 ppm in river water downstream from industrial sources.

Jungclaus, G. A.; Lopez-Avila, V.; Hites, R. A.
Organic compounds in an industrial wastewater: A case study of their environmental impact
Journal: Environ. Sci. Technol. 12:88-96

COMPOUND: alkyl phthalates

TYPE OF TEST: contamination of sediments

FINDINGS: Study found phthalate concentrations in sediments up to 56 ppm.

Office of Toxic Substances (OTS)
A study of industrial data on candidate chemicals for testing
Washington, DC: U.S. Environmental Protection Agency Contract No. 560/5-78-002

COMPOUND: alkyl phthalates

TYPE OF TEST: contamination of sediments

FINDNGS: Dialkyl phthalates have half-lived in sediments exceeding one year.

Hrudey, S. E.; Sergy, G. A.; Thackeray, T.
Toxicity of oil sands plant wastewaters and associated organic contaminants
Journal: Water Pollut. Res. Can. 11:34-45

COMPOUND: Di-n butyl phthalate (DBP)

TYPE OF TEST: 96-hour static bioassay

EXPERIMENTAL SUBJECT: rainbow trout (Salmo gairdneri Richardson)

DOSE: LC_{50} of 1.2 mg/l

FINDINGS: Acutely toxic

QUOTE: "DBP indicated sufficient acute lethal toxicity to warrant further consideration."

Hrudey, S. E.; Sergy, G. A.; Thackeray, T.
Toxicity of oil sands plant wastewaters and associated organic contaminants
Journal: Water Pollut. Res. Can. 11:34-45

COMPOUND: bis(2-ethylhexyl) phthalate (BEHP) (or DEHP)

TYPE OF TEST: 96-hour static bioassay

EXPERIMENTAL SUBJECT: rainbow trout (Salmo gairdner Richardson)

DOSE: LC of 540 mg/l

FINDINGS: Acutely toxic

Pearl, Daniel S.; Quest, John A.; Gillis, Richard A.
Use of various solvents to study the effect of diazepam on cardiac rhythm
Journal: Toxicol. Appl. Pharmacol. 44:653-656

COMPOUND: Dimethyl-formamide (DMF)

TYPE OF TEST: intravenous administration

EXPERIMENTAL SUBJECT: cats

DOSE: 57% solution: 1) increments to 1.5 ml; and 2) single dose of 0.2 ml

FINDINGS: Produced toxic cardiovascular effects

QUOTE: "DMF administered alone caused either fatal hypotension or ventricular fibrillation."