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## Discussion

Dr. H. Buchter (*University of Cologne, Germany*): It would seem better for statistical investigations on the reported liver function tests if you could compare the results with similar tests done before the workers came into vinyl chloride manufacturing. Second, in one of the two plants in Germany with incidence of vinyl chloride disease, there is much alcohol intake in the workers. Until now no liver damage has been found.

Third, in regard to low lung-function tests, we have not confirmed a pathological diagnosis at all.

There should be more discussion about the cause of this disease, i.e., whether it is vinyl chloride alone or another agent which may get together with technical vinyl chloride, or vinyl acetate or additives. This may be important in the causation of angiosarcoma.

Last, it has been suggested that liver biopsy be done only after peritoneoscopy because of the risk of bleeding.

Dr. M. L. Newhouse: May I ask Dr. Lelbach how he selected his patients and how big was the exposed group he selected them from?

Dr. W. K. Lelbach (*University of Bonn, Germany*): I will begin with the answer to the second part of the question. The whole group is, as far as we know, about 180 workers in this plant. We were alerted in December 1972 by Dr. Veltman's group that patients being examined for skin and bone disease also had signs of liver disease. We examined these patients.

Later we examined all patients we could bring to the clinic. It is, of course, a selected group and does not permit us to draw conclusions as to percentages.



B. Experimental Studies

# PRELIMINARY STUDIES OF THE FATE OF INHALED VINYL CHLORIDE MONOMER IN RATS*

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## Introduction

Vinyl chloride monomer (VCM), extensively used for the production of polyvinyl chloride and other plastics, has been associated with the development of angiosarcoma and portal cirrhosis of the liver as well as other untoward effects in workers exposed to unknown but undoubtedly high concentrations of VCM. Angiosarcomas, zymbal gland carcinomas, and nephroblastomas developed in rats exposed to concentrations of VCM ranging from 50–10,000 ppm, 4 h/day, 5 days/week for 12 months, and subsequently maintained and observed until death.[1]

No information is available on the fate of VCM in the mammalian organism at the present time. Such information is essential for elucidating the toxicodynamics of VCM and providing a rationale to assess the potential hazard of exposure to low levels of VCM. Results of preliminary studies on the fate of VCM in rats exposed via inhalation are reported herein. Prior to undertaking these studies we conceived the idea that VCM might be metabolized via the alcohol dehydrogenase pathway, and if so, this pathway would very likely be saturable, and that conjugation of VCM or its metabolites with glutathione and cysteine might be expected. Therefore, much of the work conducted to date has been directed at evaluating these possibilities.

## Methods

### *Kinetic Studies of the Uptake (Metabolism) of* *hloride Monomer*

Male Sprague-Dawley albino rats of Spar ng from 165–200 g were exposed to initial concentrations of VC rom 50.5–1167.0 ppm (0.13–2.99 mg/liter). Exposures ranged 3 min. Figure 1 depicts the closed, recirculating 4.7-liter inhala which a group of 4 rats were concurrently exposed. To minimi of fur and skin, only the nares of the rats protruded through a ie into the chamber. Expired carbon dioxide was continuousl the chamber by absorption on an Ascarite column in the recirc s carbon dioxide was removed from the system, the pressure d by a mercury manometer fitted with a photoelectric cell. Tl lenoid valve and dual syringe pump to inject makeup oxygen int

The chamber atmosphere was continuously M (10.9 $\mu$) by an in-line Miran-1 infrared analyzer (Wilks). Wit trations of VCM



* These studies were supported in part by a grant from the Manufacturing Chemists Association.

# Toxic and Health Effects of Plastics and Resins

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Twenty-five years ago a discussion of the toxic and health effects of plastics and resins would have been relatively easy on 2 counts. There were relatively few synthetic plastics and resins in common use, and such uses as were common were relatively trivial in comparison with competitive materials.

World War II gave great impetus to the use of synthetic plastics and resins. On the one hand they were able to replace natural materials, particularly metals and natural rubber, which were often in short supply. On the other hand synthetic materials, e.g., nylon, turned out to be superior to available natural materials for certain uses.

Following World War II, plastics inevitably assumed a greater role in peacetime applications. Many of the plastics were not suited to these uses, and things made of plastic were often looked down upon as poor substitutes for the genuine article. This situation, however, soon worked itself out. For one thing, there were important developments in technology, and the synthetic plastics and resins actually became better materials. For another, their proper spheres of usefulness were better recognized, so that the right plastic was selected to fill a given need.

It is difficult to define plastics and resins in a very meaningful way. Chemically, they are very large molecules, called polymers, formed by the linking up of small molecules, called monomers, into large cohesive chain-like units. If only 1 monomer is involved in forming the polymer, it is called a homopolymer. If 2 different monomers are involved, the polymer is called a copolymer; if 3, a terpolymer, etc.

Polymers can be classified in several other ways. If the monomers simply link up into long chains by joining bonds, and nothing is eliminated in the process, the polymer is called an addition polymer. An example is shown in Figure 1.

If the linking up of monomers is accomplished by the elimination of part of the monomeric molecules, the resulting polymer is called a condensation polymer. An example is shown in Figure 2.

If the long-chain polymer molecules are not joined laterally to one another, the plastic or resin is usually flexible, because the molecular chains slide against each other when a deforming force is applied. This flexibility can be increased by mixing in

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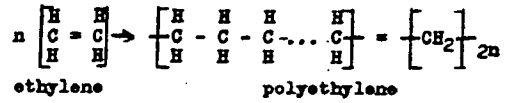


Fig. 1.—Addition polymerization.


Fig. 2.—Condensation polymerization.

TABLE 1.—*Thermoplastic Polymers*

| |
|---|
| Polyethylene |
| Polystyrene |
| Polyacrylates |
| Polymethacrylates |
| Polyvinyl chloride |
| Polyamide (nylon) |
| TFE fluorocarbon resins |
| Saturated polyesters ("Dacron") |

TABLE 2.—*Thermosetting Polymers*

| |
|---|
| Phenol formaldehyde resins |
| Amine formaldehyde resins |
| Epoxy resins |
| Alkyd resins |
| Unsaturated polyester resins |

with the polymer molecules an internal lubricant, known as a plasticizer.

It is characteristic of polymers that they soften when exposed to heat and when soft can be made to flow and assume desired shapes. When cooled, they again become hard. Some polymers, if reheated, become soft again; these are the thermoplastic resins. Other polymers, when heated for the first time, undergo further chemical reactions in which cross links develop between polymer chains, holding them rigid in the position assumed as a result of the first heating. These are the thermosetting resins, and they do not soften on reheating like the original polymer. Examples of thermoplastic and thermosetting resins are shown in Tables 1 and 2.

When we say that polymers are chains of large molecular weight, no particular degree of largeness is specified. If only a few molecules are linked together, the resultant molecule is called an oligomer. So, a polymer is larger than an oligomer in that it contains many rather than a few monomer units.

It is also apparent that a polymer may be composed of polymer chains of varying length. When a monomer polymerizes, a chain builds up in length until something terminates the process. Termination may occur sooner in some chains than in others. If the process is random, the final polymer will be a statistical distribution of molecular chains of varying size, and the molecular weight of the resultant mixture can only be expressed in terms of average and standard deviation, of normality or skewness of distribution, etc. In general, the average molecular weight of the polymer will be of the order of thousands or millions.

It has frequently been stated of the plastics and resins that the molecules are so big and so chemically inert that they are also physiologically inert. If ingested, they are too big to be absorbed from the gastrointestinal tract and hence pass through unchanged. If placed in contact with the skin, they are too big to penetrate or react with the skin. If inhaled as dust, they behave as typically "inert" dusts do in the lung. These statements are in all probability true for most of the molecules comprising the polymer. The exceptions relate in general to the oligomers, and in some cases even to the monomers, which make up a small fraction of the total polymer molecules.

For example, polyethylene manufactured by the high-pressure process came into use as a container for foods about 1946. The average molecular weight of the polymer usually ranged from 5,000 to about 40,000. Its structure is essentially that of a long-chain aliphatic hydrocarbon. It is insoluble in almost all solvents at room temperature, although it swells in contact with hydrocarbon solvents like hexane or heptane, benzene, lubricating oils, and the like. The swelling is due to the penetration of the polymer chains by the solvents. It is no wonder that the U.S. Food and Drug Administration in 1951 listed polyethylene as a suitable resin for use as a food packaging film[1] on the basis of its structure and physical properties.

By the summer of 1958, however, the Food and Drug Administration learned that commercial polyethylene contained a low molecular weight fraction that might become a component of a fatty food contacting the polyethylene. When the Food Additives Amendment of 1958 became effective, the Food and Drug Administration confirmed the prior sanction status of polyethylene as

$$n\ \underbrace{[HNCH_2 \cdot (CH_2)_4 \cdot CO]}_{\text{epsilon-caprolactam}} \longrightarrow \underbrace{H[NH \cdot (CH_2)_5\ CO]_n OH}_{\text{Type 6 Nylon}} + (n-1)\ H_2O$$

Fig. 3.—Type 6 nylon, polyepsiloncaprolactam.

a food packaging resin only with respect to its use on nonfatty foods. It permitted its continued use in contact with fatty foods only on an extension-of-time basis pending further study and evaluation of the data.

The sequel to this is that all 13 producers of polyethylene in the United States assembled data on the chemical identity of the low molecular weight fraction in their various polyethylenes and on the amount extractable by fatty foods. This information enabled the Food and Drug Administration to establish specifications for polyethylenes suitable for contact with fatty as well as nonfatty foods, and a regulation setting forth the specifications was issued in June, 1961.[2]

This example merely illustrates the fact that polymer molecules are not all of the same large size and that some are small enough to be diffusible from the plastic or resin. As with polyethylene, the low molecular weight fraction is not necessarily harmful, but its safety must be evaluated.

Some plastics and resins may actually contain unreacted monomer. Type 6 nylon, which is polyepsiloncaprolactam, is an example (Fig. 3). The epsilon caprolactam monomer is water soluble, diffusible, and a weak skin sensitizer. It can be removed from the polymer by washing with hot water.[3] Phenol formaldehyde resins as well as other formaldehyde resins sometimes contain free formaldehyde in sufficient concentration to be detectable by odor. The free formaldehyde can be kept to safe limits, however, by adequate curing of the resin.

It might be well to note at this point that exposure to monomers and low molecular weight polymers is much more apt to occur during the manufacture of these materials than during their subsequent use. Thus the manufacturer is more liable to toxicity and health problems from monomers than is the user of the finished plastic or resin. In some cases, however, the plastic or resin is deliberately supplied in an incompletely polymerized state in order that the user might complete the process at the site of application. Examples of this would be the acrylic denture materials and the polyurethane insulating materials or lacquers.

In the former application, molding powder composed of polymethyl methacrylate is mixed with liquid monomer, an activator, and color. The monomer acts both as a plasticizer for the polymer and as a bonding agent as it itself is polymerized. Since methyl methacrylate monomer is a skin sensitizer, a number of dentists and dental technicians have experienced dermatitis problems. The resulting polymerized denture material, however, has rarely caused any trouble for the patients.

Polyurethane resins are likewise often supplied in "prepolymer" form for final polymerization at the site of application. A typical application is that of the polyurethane foamed insulation materials.[4]

Figure 4 shows how a typical polyurethane prepolymer (I) is formed by the reaction, in the absence of water, of a diisocyanate (usually toluene diisocyanate, or TDI) and a glycol. The glycol now terminates with isocyanate groups (-NCO) and has acquired urethane groups (-RNH · COOR'-) in the process. The prepolymer contains a slight excess of TDI.

If water and a catalyst are added to the prepolymer, a further reaction takes place as shown in Figure 5. This reaction is exothermic. As polymerization takes place the $CO_2$ evolved "foams" the mixture which grows more viscous and rigid under the combined influence of heat and increasing molecular weight and traps the $CO_2$, thus giving the final cured foam plastic. In the

$$2\ OCN\text{-}R\text{-}NCO + HO\text{-}R'\text{-}OH \longrightarrow$$

$$\underline{OCN\text{-}R\text{-}NH\cdot CO\cdot O}\ \text{-}R'\text{-}OCO\cdot NH\text{-}R\text{-}\underline{NCO}\ \ (I)$$

Fig. 4.—Reaction of diisocyanate with polyol.

$$2\ \underline{OCN}\text{---}\text{---}\text{---}\underline{NCO}\ (I) + H_2O \longrightarrow$$

$$\underline{OCN}\text{---}\text{---}\text{---}NHCONH\text{---}\text{---}\text{---}\underline{NCO}\ (II) + CO_2\uparrow$$

Fig. 5.—Polymerization of polyisocyanate resin.

process, small amounts of TDI monomer may be volatilized.

Toluene diisocyanate is not a highly toxic material, but it is extremely irritating to the respiratory tract and may cause asthma-like attacks which begin several hours after exposure and clear up without after-effects in a few more hours. Repeated exposure to TDI vapors may produce an allergic sensitization of the respiratory tract in susceptible individuals.

Since polyurethane resins are being formed in place on a rather large scale, there has been an unusual amount of interest in the definition of the safe upper limit of concentration of the monomer in the air, variously called the Threshold Limit Value, Hygienic Limit, or MAC. Largely based on work in Du Pont's Haskell Laboratory,[4] the American Conference of Governmental Industrial Hygienists (ACGIH) in 1956 established a tentative Threshold Limit Value of 0.1 ppm for toluene diisocyanate, TDI, and this has prevailed until this year when the ACGIH lowered the Threshold Limit Value to 0.02 ppm. It may be of current interest to comment briefly on the respective numbers and the reasons for the change.

Bearing in mind that TDI and other similar monomeric diisocyanates are more irritating than toxic and that they are capable of producing allergic sensitization, the safe level in the atmosphere should be that which does not produce primary irritation or induce sensitization of exposed workers. Our estimate of such a level, based on animal exposures, was 0.1 ppm, and Ehrlicher in Germany[5] arrived independently at the same value. Some cases of respiratory sensitization have occurred, however, in some plants in which the TDI concentration was supposedly maintained at or below 0.1 ppm. It was assumed, therefore, that susceptible workers exposed to 0.1 ppm of TDI could become sensitized, and the safe upper limit was, accordingly, revised downward to 0.02 ppm.

Whether the assumption is valid and the revision justified, I do not know. So far as I have been able to learn, there is no proof that sensitized workers did not occasionally receive gross overexposures prior to becoming sensitized. Only time will tell whether 0.02 ppm will prove to be a more correct estimate of the safe level than 0.1 ppm.

The important point, however, is that one should avoid, to the greatest extent possible, exposure to chemicals which are capable of causing allergic sensitization. It is a tricky business, for example, to find out just how much poison ivy you can pull up with your bare hands before you become sensitized, and persons exposed to the monomeric diisocyanates should take all indicated precautions to keep their exposure at a minimum.

The finished cured polyurethane resins are not sensitizers, because any exposed isocyanate groups would react with water vapor in the air and be destroyed.

A second health and toxicity problem in connection with plastics and resins arises from the fact that the commercial materials are seldom *just* collections of big molecules. As was mentioned before, flexibility in plastics is a reflection of the ability of individual polymer chains to slide against each other in response to an applied force. The cohesive forces between polymer chains can be reduced by means of internal lubricants called plasticizers. Usually a *good* plasticizer can be characterized as a *poor* solvent for the polymer, which possesses low volatility and hence is not lost quickly from the plastic or resin. Sometimes plasticizers are supplemented by nonvolatile liquids which are not in themselves plasticizers but which can supplement the effect of plasticizers by acting as inert diluents. These are called softeners.

Plasticity can also be enhanced, however, in some polymers by copolymerization of the principal monomer with a small amount of a second monomer which, while a fixed

part of the polymer chain, acts as an internal plasticizer.

Unplasticized polyvinyl chloride, for example, is a rather rigid material and can be used for such applications as pipes for water or process chemicals. When plasticized by the addition of organic phthalate, sebacate, or phosphate esters, however, it becomes quite flexible and can be used for such things as raincoats, shower curtains, and automobile upholstery. Perhaps you will recall an early use of the plasticized copolymer of vinyl chloride and vinyl acetate for transparent wrist watch bands, garters, and suspenders and will recall the dermatitis which was attributed to the use of dibutyl tin maleate and dibutyl sebacate as plasticizers.[6] The example both points up the fact that nonpolymeric components of a plastic can become health or toxicity problems and testifies to the skill with which such toxic components have since been carefully excluded from plastics which are likely to come into prolonged or repeated contact with human skin or with food products.

Plasticizers are not the only materials added to plastics and resins to modify their properties. Chemicals are sometimes added to stabilize the polymer against decomposition by light or heat. Others may be added to retard oxidation by atmospheric oxygen. Dyes or pigments may be added to impart color. Perhaps this complexity of plastics and resins can be illustrated by reference to the *Federal Register* of Aug. 8, 1961, establishing a regulation on permissible ingredients for continuous resinous and polymeric coatings to be used on metal substrates (i.e., can liners) in contact with foods. It amply indicates the fact that plastics and resins may be more complex than just polymers and that we must consider molecules other than polymers in evaluating health and toxicity problems relating to such plastics and resins. It is fair to state that such toxicity and health problems which have arisen in the past from the use of plastics and resins have been overwhelmingly due to the nonpolymeric components rather than to the basic polymers.

There is another area, however, in which health problems have arisen in connection with plastics and resins, and this concerns not the plastics and resins as such but rather their decomposition products under the influence of heat.

One of the earliest indications of hazard from this source came from the Cleveland Clinic disaster of 1929, in which stored nitrocellulose base x-ray film caught fire. Dense brown fumes spread through the hospital, and 125 persons were killed. Death appeared, in most cases, to have been caused by inhalation of carbon monoxide and nitrogen oxides,[7] both of which were thermal decomposition products of nitrocellulose.

Nitrocellulose is an outstandingly hazardous material so far as combustion is concerned, but it is characteristic of organic polymers that they will begin to decompose at some critical temperature and thereafter decompose at an increasing rate as the temperature is raised above the critical temperature. Some, like nitrocellulose, will burn freely if ignited; others, like Teflon TFE-fluorocarbon resin will not burn spontaneously but will nevertheless decompose if sufficient heat is applied externally. As plastics and resins find more extensive use as replacements for older materials, it is natural that there be increasing concern lest exposure to excessive heat or fire result in the production of unusually toxic atmospheres.

It will not be possible to cover the pyrolysis products of all plastics and resins in this discussion, but mention will be made of some general principles pertaining to the toxicity of the products arising from any conflagration. Specific mention will be made of polyethylene, of the synthetic textile material Orlon acrylic fiber, of certain foamed plastics and natural rubber, and of the Teflon TFE fluorocarbon resins.

Conflagrations can be divided broadly into 2 classes, those which are well ventilated, and those which are poorly ventilated.

A well-ventilated conflagration is one in which there is free access of air to the fire. In this event the gaseous products of combustion are dissipated rapidly by the strong thermal currents, and injury, if it occurs, is almost always due to thermal effects alone.

A poorly ventilated conflagration is one in which the access of air is restricted. In this case, there are several consequences. First, combustion does not go to completion. If the combustible material contains carbon, as it usually does, carbon monoxide will be formed as well as carbon dioxide. Second, there will be a depletion of oxygen in the air in the vicinity of the fire. Third, there will be heat. And finally, there will be special pyrolysis products characteristic of the substances being burned. If injury occurs, it will be due to heat, oxygen lack, and carbon monoxide as well as to the special pyrolysis products. It is my belief, which is based on World War II research with flame throwers,[8] that the 3 factors heat, oxygen lack, and carbon monoxide are usually of more overriding importance as toxic factors than the more esoteric special products of combustion.

Of course, there may be situations, as in the Cleveland Clinic disaster, where the products of a poorly ventilated combustion may be transported some distance by natural or forced ventilation, and in these cases, heat ceases to be a significant lethal factor. This does not invalidate the generalization that gaseous products of combustion are of little importance as lethal factors in a well-ventilated conflagration and that carbon monoxide, oxygen lack, and heat are apt to be the most important lethal factors in a poorly ventilated conflagration, regardless of what material is being burned.

Polyethylene may be taken as a particularly simple example, in the chemical sense, of a plastic ( resin; it is made up of chains of $CH_2$ gı ıps and is therefore a hydrocarbon. It rese ıles the paraffin waxes but is less of a hete geneous mixture than the paraffin waxes. t burns slowly in an excess of air, produ ng $CO_2$ and $H_2O$ as the end-products c combustion. If the burning were poorly ventilated, combustion would be incomple and CO would be produced as well as $O_2$. If polyethylene is heated in air to out 250 C it melts, sublimes, and to a d ree decomposes without burning. Animal exposed to air passed over the heated poly hylene show signs of respiratory distress and may die. The causative lethal age or agents were not identified in experir nts which we carried out some years ago ut it was noted that the air containing the ecomposition products of polyethylene wo l decolorize a dilute solution of potass m permanganate if bubbled through it. his would suggest the presence of unsatı ıted compounds like aldehydes, which a also formed during the pyrolysis in air c natural hydrocarbons.

In summary, poly hylene would present roughly the same he th and toxicity problems on combustior or pyrolysis as one would expect from raffin wax or similar natural hydrocarbons

Orlon polyacrylo rile may be looked upon as a polyethyle : in which 1 of the 4 hydrogens is replac by a nitrile group. (Fig. 6). The pre nce of the multiple cyanide groups on t : polymer, as well as the considerable tox ity of the monomer, raised the question to whether the combustion of Orlon m ght not result in the release of dangerous uantities of HCN or of acrylonitrile. The Underwriters' Laboratories undertook an investigation of this point.[9] In one type of experiment Orlon fabrics were subjec l to direct flame in the presence of exc s or deficient air. In

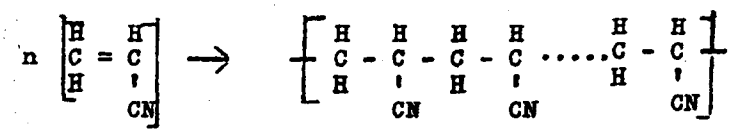


Fig. 6.—Orlon polyacrylonitrile.

another type, the Orlon fabrics were heated in an atmosphere of nitrogen in an electric furnace which reached a peak temperature of 600 C. In both types, gaseous decomposition products were collected and analyzed. Similar tests were carried out with fabrics of cotton, silk, acetate and viscose rayon, and wool.

The conclusions of the Underwriters' Laboratories with respect to Orlon acrylic fibers were as follows:

When these acrylic fiber fabrics burn in an excess of air (oxygen excess), the chief constituents of the gaseous products of combustion and thermal decomposition include carbon dioxide, together with small amounts of oxides of nitrogen as recorded in Table V. Under conditions of oxygen deficiency, the combustion and decomposition products of the acrylic fiber fabrics include carbon dioxide, and small amounts of carbon monoxide, hydrocyanic acid, ammonia, and oxides of nitrogen. When the acrylic fiber fabrics are subjected to thermal decomposition (pyrolysis) in atmospheres of nitrogen (air absent) the volatile products include relatively large amounts of hydrocyanic acid, ammonia, hydrogen and methane, together with smaller amounts of unsaturated hydrocarbons as shown in Table VI.

Both silk and wool behaved similarly to the Orlon fabrics in that relatively large amounts of HCN were evolved only when the pyrolysis was carried out in a nitrogen atmosphere. The final conclusions of the Underwriters' Laboratories were as follows:

The fire hazards of textile fabrics made from these acrylic fibers are in a class with those presented by cotton, acetate rayon, and viscose rayon fabrics of similar weight and weave.

The life hazards of the combustion and thermal decomposition products of these acrylic fiber fabrics under fire conditions are judged to be similar to those presented by the fumes evolved during combustion or thermal decomposition of silk or woolen fabrics.

TABLE 3.—*Pyrolysis of Elastomeric Foams at 200 C for 6 Hours*

| Foam | Sample Wt., Gm. | % Wt. Loss | Mortality |
|---|---|---|---|
| Polyurethane A | 5.07 | 5.3 | 0/4 |
| Polyurethane B | 5.03 | 4.6 | 0/4 |
| Polyurethane C | 5.07 | 3.6 | 0/4 |
| Neoprene | 5.53 | 8.1 | 0/4 |
| Rubber latex | 5.03 | 3.5 | 0/4 |
| Polyvinyl chloride | 4.70 | 43.2 | 2/4 |

This illustrates several things. The synthetic fiber material Orlon polyacrylonitrile, like other plastics and resins, does decompose under the influence of heat; its decomposition and combustion products are toxic. But the same statements apply to the natural polymers silk and wool and cotton, and the over-all hazard from the combustion and decomposition of Orlon is judged to be similar to that from silk or wool. The substitution, therefore, of a synthetic plastic or resin for a natural one does not necessarily increase the hazard that already existed with respect to the natural materials.

A similar question arose about the safety of various synthetic foam plastics as compared with natural rubber. To answer this question we carried out experiments with foamed polyurethane, polyvinyl chloride, neoprene, and natural rubber.[4] The results are shown in Tables 3, 4, and 5.

It can be seen from Table 3 that polyvinyl chloride foam was the least thermostable, in that it experienced 43% weight loss and killed 2 of 4 rats at an exposure temperature of 200 C. Foamed polyurethane, neoprene, and natural rubber all decomposed to a certain extent at 250 C, and all produced some deaths in exposed animals (Table 4). At 560 C decomposition was essentially complete within 10 minutes except for neoprene (Table 5). Since the samples were smaller in this case than in the exposures at 200 C and 250 C, no deaths occurred except for 1 animal exposed to polyvinyl chloride. In all cases death was due to pulmonary congestion and edema regardless of the foamed resin responsible.

Again it can be seen that certain synthetic foamed plastics and resins are similar to a

TABLE 4.—*Pyrolysis of Elastomeric Foams at 250 C for 6 Hours*

| Foam | Sample Wt., Gm. | % Wt. Loss | Mortality |
|---|---|---|---|
| Polyurethane A | 6.85 | 40.8 | 1/4 |
| Polyurethane B | 6.20 | 20.5 | 1/4 |
| Polyurethane C | 6.72 | 26.5 | 0/4 |
| Neoprene | 5.67 | 45.4 | 1/4 |
| Rubber latex | 6.01 | 16.0 | 4/4 |

TABLE 5.—*Pyrolysis of Elastomeric Foams at 560 C for 10 Minutes*

| Foam | Sample Wt., Gm. | % Wt. Loss | Mortality |
|---|---|---|---|
| Polyurethane A | 2.00 | 100 | 0/2 |
| Polyurethane B | 2.00 | 97.3 | 0/2 |
| Polyurethane C | 2.00 | 100 | 0/2 |
| Neoprene | 2.00 | 75.4 | 0/2 |
| Rubber latex | 2.00 | 93.5 | 0/2 |
| Polyvinyl chloride | 2.00 | 95.7 | 1/2 |

foamed natural product with respect to hazard from thermal decomposition products. A history of safe use of the natural product would imply that a similar history of safe use could be anticipated for the synthetic materials.

One should not make the assumption that all synthetic plastics and resins will be as safe as any natural material they might replace. But neither should one assume that the natural materials give harmless pyrolysis products because they have proved to be free from a practical hazard in actual use. In judging the safety of a synthetic resin for a proposed use, the hazard from combustion or thermal decomposition should be compared under equivalent conditions with that of alternative materials which have, if possible, a history of similar use.

Finally, it may be of interest to discuss briefly the hazards of combustion or thermal decomposition of the Teflon TFE fluorocarbon resins, both because the volume of our correspondence indicates a lively current interest in them and because of certain interesting features of the story.

TABLE 6.—*Acute Toxicity of Tetrafluoroethylene*

| Structure | Acute Inhalation Toxicity for Rats $LC_{50}$, ppm* |
|---|---|
| $CF_2=CF_2$ | 40,000 |

* Data from studies at Haskell Laboratory; 4-hour exposure.

The Teflon TFE fluorocarbon resins are analogs of polyethylene in which all of the hydrogens of polyethylene are replaced by fluorine atoms. The monomer, tetrafluoroethylene, while more toxic than ethylene, is still quite low in toxicity, the $LC_{50}$ being 40,000 ppm for 4-hour exposure of rats (Table 6). It polymerizes readily to polymers of very large molecular weight, which are characterized by their extreme chemical inertness and thermostability. Male and female weanling rats in our laboratory fed diets containing 25% of finely ground Teflon TFE resins for 90 days showed no signs of toxic effects and no pathological changes detectable by gross or microscopic examination of the tissues.

Teflon TFE resins are among the most thermostable of all the synthetic plastics and resins, being rated for continuous use at 260 C. At this temperature the weight loss is from 0.0001% to 0.0006% per hour (Table 7), depending on the type resin. Since the TFE resins soften at 327 C, the melting point of lead, they are not likely to be serviceable for continuous use at or above this temperature, but they can stand brief exposures for short periods of time to temperatures as high as 540 C. The TFE

TABLE 7.—*Weight Loss and Ventilation Recommendations for Teflon Fabricated Resins Above 450 F*

| Temperature | | Initial Weight Loss, %/Hr | | | Air Recommendations Cu. Ft/Min/Lb Resin | | |
|---|---|---|---|---|---|---|---|
| F | C | Teflon 1, 5, 7-TFE Resin | Teflon 6, 30-TFE Resin | Teflon 100-FEP Resin | Teflon 1, 5, 7-TFE Resin | Teflon 6, 30-TFE Resin | Teflon 100-FEP Resin |
| 450 | 230 | 0.00005 to 0.0001 | 0.0001 to 0.0002 | 0.0004 | 0.12 | 0.50 | 0.86 |
| 500 | 260 | 0.0001 | 0.0006 | 0.001 | 0.21 | 1.3 | 2.1 |
| 550 | 290 | 0.0003 | 0.0015 | 0.01 | 0.66 | 3.5 | 21 |
| 600 | 320 | 0.0005 | 0.0045 | 0.02 | 1.2 | 10 | 42 |
| 650 | 340 | 0.0018 | 0.014 | 0.08 | 4.2 | 33 | 180 |
| 700 | 370 | 0.004 | 0.032 | 0.3 | 9 | 73 | 650 |
| 750 | 400 | 0.008 | 0.08 | | 18 | 180 | |
| 800 | 425 | 0.15 | 0.15 | | 325 | 325 | |

Note: Air recommendations represent the volume of air to reduce gaseous products to levels found safe through long experience in processing Teflon resins.

resins do not liquefy on exposure to heat but decompose by giving off gases and particulate matter commonly referred to as sublimate. If thermal decomposition is carried out in the absence of air, more than 95% of the decomposition products is the monomer, tetrafluoroethylene.[10] If carried out in the presence of air, the monomer is still the major decomposition product, but at temperatures from 200 C to 400 C small amounts of other fluorocarbon gases of 3 to 5 C atoms, HF, and silicon tetrafluoride have been detected. At about 400 C small amounts of a highly toxic $C_4$ compound, perfluoroisobutylene, begin to appear, but this gas has not been detected below 380 C.[11,12]

Teflon TFE resins can be ignited by flame, since the gaseous decomposition products will burn at 690 C, but once the flame source is removed, the Teflon itself will not continue to support combustion. The ultimate combustion products are $CO_2$, $CF_4$, and HF. No free fluorine gas has been detected among the pyrolysis or combustion products of Teflon, and its formation is not favored by thermodynamic considerations.[12]

All of the above would lead one to conclude that heated Teflon TFE resins should not present an appreciable life hazard, and this has been borne out both by laboratory experiment and by a history of use covering more than a quarter of a century. To the best of our knowledge, no one has ever been killed by exposure to the thermal decomposition or combustion products of the Teflon resins.

However, the Teflon resins do present on exposure to heat a unique toxicity and health problem which became evident even before the product became commercial. Sufficiently hot Teflon gives off something which when inhaled produces in man a condition like metal fume fever. It has been variously called polymer fume fever[13] or "the shakes." Like metal fume fever, it resembles influenza so far as symptoms are concerned, and it passes off without treatment or after-effects in a matter of hours or at most a day or two. In most cases its occurrence has followed the smoking of tobacco contaminated with dust or particles of Teflon. In the minority of cases it has followed close proximity to freshly sintered Teflon articles as they have been removed from the sintering oven.

In the ordinary course of events one would study polymer fume fever in the laboratory by producing it in experimental animals breathing air drawn over Teflon resins heated to various temperatures. One would find the lowest temperature at which the syndrome occurred, and one would analyze the pyrolysis products at that temperature and would identify by the process of elimination the causative agent. One could then determine the threshold concentration of the agent needed to produce the polymer fume fever and could then estimate a Threshold Limit Value or MAC for man. Unfortunately, experimental animals do not get polymer fume fever any more than they get metal fume fever, so this avenue of approach was closed.

On a priori grounds, one could assume that the likelihood of getting polymer fume fever would depend (1) on the temperature of the Teflon resin, because this determines the decomposition rate; (2) on the quantity of Teflon being heated, because a large quantity of Teflon at a given temperature might release as much of the causative agent as a smaller quantity of Teflon at a higher temperature, and (3) on the time duration of exposure, since this would determine the amount of contaminated air taken into the lungs.

Since industrial processors of Teflon resins may handle many pounds per day, it was felt that a conservative recommendation would be that one should provide ventilation if Teflon were heated above the temperature at which pyrolysis is just detectable. This was estimated to be roughly 200 C or 400 F. At or below this temperature the quantity of Teflon handled and the exposure time should be irrelevant, since the Teflon simply wouldn't be giving off pyrolysis products. This, then, was the basis for Du Pont label warnings to provide

TABLE 8.—*Mortality Ratios Resulting from the Toxicity Tests on Various Polymer-Insulated Wires*

| Wire Insulation | Pyrolysis Temperature 200 C | 250 C | 300 C |
|---|---|---|---|
| Silicone rubber | 0/2 | 0/2 | 2/2 |
| Nylon-polyvinyl chloride | 0/2 | 0/2 | 0/2 |
| Polyvinyl chloride | 0/2 | 0/2 | 0/2 |
| Kel-F | 0/2 | 0/2 | 2/2 |
| Teflon 6 | -- | 0/2 | 2/2 |

ventilation or respiratory protection if the Teflon were heated above 200 C or 400 F. It was directed to people handling large quantities of Teflon in industry. For such purposes the recommendation is adequate but perhaps overconservative, because the 2 conditions under which polymer fume fever is known to occur involve much higher temperatures, 370-430 C in the sintering operations and perhaps up to 538 C in burning tobacco. On the other hand, the quantity of Teflon consumed in a burning cigarette was bound to be small and yet was capable of evoking the syndrome.

In the intervening years little more has been learned about polymer fume fever. We now suspect that the causative agent has a very brief life time and that a short travel path from source to lung, ideally, as in smoking, is an important factor. We have obliged a dog to "smoke" repeatedly through a face mask cigarettes containing up to 200 mg. of Teflon. It produced neither the polymer fume fever nor any other observable harmful effect. We conclude from this that there is a wide margin of safety between the quantity of Teflon producing the polymer fume fever in man and that which might cause more drastic or lethal effects. We are inclined to suspect the particulate matter evolved during the pyrolysis of Teflon more than the gases, simply because metal fume fever is caused by a particulate.

It would undoubtedly be much more satisfying if we could both identify the causative factor of the polymer fume fever and assign an MAC value to it. The American Conference of Governmental Industrial Hygienists has, in fact, made 2 attempts to supply at least a number. In 1960 they assigned a tentative threshold limit value of 0.005 ppm to Teflon pyrolysis products without specifying what products. In the 1961 list the tentative value is 0.05 mg. per cubic meter "as F." I know of no scientific basis, however, for either of these numbers.

In a laboratory situation one can, of course, kill animals by exposing them to the pyrolysis products of Teflon resins. Table 8 compares the toxicity of the pyrolysis products of Teflon and other resins used as wire insulation materials. The toxicity of the

TABLE 9.—*Per Cent Mortality in Animals* Exposed to Pyrolysis Products from "Teflon" 6 TFE Resin*

| Sample No. | Pyrolysis Temperature, C 300 | 350 | | 375 | 400 | 425 |
|---|---|---|---|---|---|---|
| OF-6 | -- | 25 | | -- | -- | -- |
| OF-7 | 0 | 75 | ♂ Rats | -- | -- | -- |
| | | 100 | ♀ Rats | | | |
| | | 0 | Mice, Rabbits, Guinea pigs | | | |
| EF-1 | 0 | 6 | | 63 | -- | -- |
| EF-2 | -- | 0 | | -- | -- | -- |
| EF-3 | 0† | 0† | | -- | 0† | 100 |
| EF-4 | -- | -- | | -- | 0 | 50‡ |
| | | | | | | 0 |

* Unless otherwise indicated, mortality figures are for rats.
† Exposure included 30 ♂, 3 ♀ rats; 10 ♀ mice; 4 ♂ guinea pigs; 1 ♂, 1 ♀ rabbit.
‡ One of two guinea pigs died.
OF indicates production prior to 1958; EF, current production.

Teflon resins is not outstanding. It is interesting also that improvement in processing techniques over the past few years has made it possible to prepare tetrafluoroethylene monomer of higher purity than heretofore and has resulted in a significant increase in the temperature at which the polymer can kill laboratory animals. This is shown in Table 9.

There is one other item about the health and toxicity hazards of the Teflon resins which illustrates a human frailty rather than a property of the resin. Sometime in the middle 1950's there arose a rumor that a machinist had smoked a cigarette contaminated with a little Teflon and had subsequently died. In its most extreme form the rumor stated that the machinist took one puff and that his lungs filled up with fluid, and he died within 5 minutes. It is interesting that the vehicle by which this rumor spread was official safety bulletins issued by responsible industrial concerns and by military installations. In no case did a bulletin state that the fatality had occurred in the company or installation issuing the bulletin. An aircraft plant on the West Coast, for example, attributed the incident to a certain eastern Air Force installation. Another Air Force installation attributed it to the aircraft plant on the West Coast. In no case were we able to pin down the alleged event to an actual occurrence. In 1958 the Inspector General, U.S. Air Force, issued the following statement:

"Although the rumor appeared in several local Air Force publications, a complete investigation by the Air Force Medical Service has proved it to be completely unsubstantiated. There is no known case of Teflon toxicity which has occurred in Air Force or Air Force-Contractor facilities." [14]

Within the past 12 months the same old rumor has enjoyed a remarkable resurrection. It appeared, for example, in at least 3 safety bulletins issued in the Pittsburgh area as well as in other sections of the country and again including some Air Force installations. The features were identical with the earlier cycle. The alleged death never occurred in the facility issuing the bulletin, whose authors copied the story from someone else's bulletin or based it on verbal information from someone who had seen or heard of such a bulletin. One company quite recently copied the story from a bulletin long since disavowed by its originators and sent 137 copies of its version to locations in the United States, Canada, and Mexico. And while this company states that each of these locations has since received a retraction, one can predict that the original will live longer than the retraction. On July 13, 1961, and again on Oct. 20, 1961, the U.S. Air Force reiterated, in a message to all Air Force installations, the fact that the rumor had never been substantiated in spite of thorough investigation.

But in spite of all this, the rumor marches on. The latest example, to my knowledge, appears in the Oct. 21, 1961, issue of the *Canadian Medical Association Journal* [15] as a letter to the editor over the signature of an industrial physician from British Columbia. This letter contains verbatim chunks from a safety bulletin issued in New York in October, 1960, and rescinded in December, 1960. The author states that his information is derived from a publication of the British Columbia Fire Chiefs' Association, and he apparently was unaware of the ultimate source of his words. The *Journal* editorialized on the letter, commenting, "When a hazard is reported. . . sufficient evidence must be given to allow the reader to judge, on the spot, whether the conclusion is justified. These criteria have been fulfilled . . . in . . . [the] letter that appears elsewhere in this issue."

The human frailty illustrated by this recital is, of course, our readiness to accept and repeat rumors without checking the facts, simply because the rumor sounds credible. It is not confined to matters of health and toxicity but is perhaps accentuated in that field, to which many popular fads and fancies bear witness. It has been encouraging, however, to find that many industrial hygienists, toxicologists, and physicians have been quick to question the

accuracy of the rumor and have been of great assistance in securing its retraction.

It has not been possible in this discussion to cover systematically the health and toxicity aspects of all of the synthetic plastics and resins, and I have sought instead to illustrate broad areas with a few specific examples. Additional information can be found in the review articles of Schwartz,[16] Harris,[17] and Wilson and McCormick,[18] as well as in the Plastics Safety Handbook[19] issued by the Society of the Plastics Industry and the National Safety Council.

As a class, the plastics and resins are not as exempt from health and toxicity problems as one might have supposed them to be on the grounds of their large molecular weight and chemical inertness. There are problems of monomers, of low molecular weight fractions, of adjuvants, and of thermal decomposition and combustion products, and we must be alert for them. The recognition of problems, however, is the first requisite for their solution, and the synthetic plastics and resins of today are much safer than their predecessors.

It is likely that plastics and resins will continue to find expanding uses in our technology. With sufficient effort it should be possible to make sure that they will be as safe as, or safer than, the older materials which they will be replacing.

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