

The Health Hazards of Plastics

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A plastic has been defined as "a material that contains as an essential ingredient an organic substance of large molecular weight, is solid in its finished state and, at some stage in its manufacture or in its processing into finished articles, can be shaped by flow. . . . The terms plastic and resin are used in overlapping senses, but resin applies more specifically to the more or less chemically homogenous polymers used as starting materials in the production of molded articles, while plastic signifies the final solid product which may contain fillers, plasticizers, stabilizers, pigments, etc."¹ Today plastics have assumed a very important place in our lives and are practically ubiquitous, being found in the home and in industry and as components of many everyday items we use. This review of the toxicology of plastics was undertaken because of their importance and widespread use.

The oldest synthetic plastic is celluloid. This is a cellulose nitrate, or pyroxyline type, whose discovery and development began with the early work of Braconnot in France in 1833 and Schoenbein in Germany in 1845. John Hyatt, an American, however, is generally credited as being the first to work with cellulose nitrate as a plastic mass rather than in solution. His work was patented in 1869. In spite of its many uses, cellulose nitrate is readily decomposed by heat and is very unstable in sunlight. Its chief hazard, however, is its extreme flammability which led to the search for other products.

The first and still important commercial synthetic resin was a phenol-formaldehyde condensation product, described and patented in 1909 in the U.S. by Bakeland. In contrast to cellulose nitrate, which was thermoplastic, the new resin, named Bakelite, was a thermosetting material. A modification of this type of material was the resorcinol-formaldehyde resin introduced in 1943 and used as a binding agent.

Cellulose acetate was the next major product developed, beginning in 1927, although it had been known for many years prior to that. The advent of injection molding presses during this period greatly increased the use of this thermoplastic material. In addition to being highly resistant to impact it was much less flammable than the original cellulose nitrate product.

Urea-formaldehyde resins were introduced commercially in 1929, and unlimited color possibilities became available with them. Light-weight and shock-resistant, they have been extensively used in the illuminating industry.

Polyvinyl esters are another group of plastics which were known for many years prior to their commercial development in the U.S. in the late 1920's. The most important of these materials are polyvinyl acetate, polyvinyl chloride, copolymers of vinyl chloride and vinyl acetate, and the polyvinyl acetals. Polyvinyl acetates are commonly used in adhesives and coatings for paper, textiles, and leather, whereas the polyvinyl chlorides are used in wire and cable coatings, packaging films, and flexible tubing. Polyvinyl butyrate has been used in laminated safety glass.

Polystyrene, one of the oldest synthetic polymers, was prepared as early as 1839, by Simon. However, it was not until 1937 that a synthetic monomeric styrene of high purity could be produced commercially and a corresponding polymeric product made. Important properties of polystyrene include its low power factor and near zero water absorption which make it particularly well suited for radio-frequency insulation work. Newer processes use copolymerized styrene with butadiene to provide high-impact-strength materials.

Cellulose acetate butyrate was first marketed in 1938, and ethyl cellulose, the first cellulose ether made in the U.S., was also developed during this period. Cellulose acetate butyrate has been used in photographic film, lacquers, and protective coating solutions, while ethyl cellulose has been used in adhesives, paper and fabric coatings, and wire insulation.

Polyamides, of which the best known is nylon, were developed between 1929 and 1936 and came into use several years later as low-density, tough, high-tensile-strength plastics.

Another group of plastics developed in 1939 was the melamine-formaldehyde resins. These have found widespread use in such areas as molded tableware products and ignition parts of aircraft engines. More recently they have been mixed with pulp products to provide wet strength for paper products.

Polyesters, the alkyd resins, were developed in the early 1940's. Light-weight and rigid, they have been incorporated into many products including ducts for air-conditioning systems, luggage, and prefabricated housing panels.

Silicones are a group of plastics which have also been recognized for many years, dating back to 1871. However, they were not commercially available until 1943. Because of their heat resistance they created a revolutionary advance in electrical insulation. Silicone rubbers, too, have been developed. The silicone resins have been used in baked coatings for protection of radiators, heat exhaust pipes, and stacks, while silicone rubber has been used as a gasket material on searchlights and aircraft.

Polyethylene, the simplest member of a large group of ther-

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moplastic resins, was patented in 1937 in Great Britain and was introduced in the U.S. in 1941. In 1946 polytetrafluoroethylene (PTFE), marketed as Teflon®, became available. It is unusually inert and resistant to all types of chemicals except molten alkali metals.

The epoxy resins, derived from ethylene oxide, its homologs or derivatives, are among the newer plastics which have been developed. The prototype of this group was made by direct polymerization of ethylene oxide, which produced a straight-chain, thermoplastic polymer. These resins have been used extensively as adhesives and in the production of protective coatings.²

The plastics which have been discussed are representative of different groups and are only a few of the many that have been and are being produced and used. From a toxicologist's viewpoint there are numerous health hazards in the manufacture and use of these plastics. This paper will deal only with hazards associated with the finished product. The hazards of manufacturing processes will not be discussed.

The health hazards of plastics can be divided into several broad areas. These include direct toxicity from oral ingestion, respirable particulate inhalation, and the toxicity of additives and unreacted chemicals; dermatological problems; acro-osteolysis; toxicity of thermal decomposition products; hazards from fillers in plastics; and toxicology in medical application. Carcinogenic potentials of plastics will be considered in the last section.

Direct Toxic Effects

It is generally accepted that plastics as a group have a moderately low order of acute toxicity as expressed by their oral LD₅₀'s, inhalation hazard, and skin irritation potentials. Certain specific exceptions to this generalization exist, and they will be discussed in this and in later sections of this paper. The purpose of this report is not to list all potential hazards for all of the existing plastics. Rather, groups of plastics will be discussed, along with the problems most frequently associated with them.

Many plastics, including polyvinyl chloride, polyvinyl acetate, polyethylene, polystyrene, and methyl methacrylate, are more or less physiologically inert.³ Acute oral LD₅₀ values are not readily available for them because they have to be administered in such large quantities that their sheer bulk effects overshadow their toxicity. This is not the case with the starting monomers which have varying degrees of toxicity associated with them. However, since this discussion will be confined to the finished plastic products, the toxicity of individual monomers will not be reviewed except where pertinent. A good review of the hazards of monomers and other reactants may be found in Patty,³ Malten and Zielhuis,⁴ and McCollister.⁵

Many papers have been written on the potential hazards of epoxy resins. In contrast to most other plastics which may be conveniently produced long in advance of their actual use, epoxy resins must be prepared immediately before being used. Because of this, the hazards associated with manufacturing the resins cannot be easily separated from those associated with the finished plastic. Epoxy resins are prepared from two materials. One is the uncured resin which is a polyether with terminal reactive epoxy groups. The other is the cross-linking or curing agent. The uncured resins possess a low order of

toxicity.⁶ Borgstedt⁷ noted some central nervous system depression with doses of 1 to 15 gm/kg of the oligomeric (uncured) resin in mice. Cornish and Block⁸ reported data on three uncured resins with acute oral LD₅₀'s ranging between 3 to 4 gm/kg. No other significant hazards have been reported with these resins.

In contrast to the uncured resins, a variety of hazards have been reported with the various curing agents used. The most frequently used cross-linking agents are the amines. Aliphatic polyamines which are commonly used include ethylene diamine, diethylene triamine, and triethylene tetramine. All are alkaline and are capable of causing extensive, corrosive tissue damage. The most commonly encountered problems arising from amines are skin rash, tenderness, and scaling. These will be discussed more fully in the next section. Another problem which commonly develops is bronchial asthma.⁹ Because the curing reaction may be exothermic, fumes from the reactants often escape and can present a hazard. Also, the cross-linking agent is frequently added in excess in order to drive the reaction to completion. This may result in unreacted amines being left in the product.⁷ Grinding, sanding, and polishing epoxy resins present other hazards, including the production of dust and fumes. Breyse¹⁰ has reviewed the health hazards from these procedures and has suggested various precautionary measures. Among these are adequate ventilation of working areas and proper personal protection, such as gloves, masks, and protective goggles for the eyes.

In more recent work the chronic oral toxicity of a number of plastics has been studied. Vinyl chloride/vinyl acetate copolymers (molecular weight 25,000 to 30,000 by the Staudinger method) fed to rats in 1.5% and 12% of their diets produced no ill effects after two years.¹¹ A chronic feeding study with polyvinyl-pyrrolidone (PVP) in dogs showed that in amounts up to 10% of their diet no ill effects were produced after two years, although PVP was tentatively identified in the lymph glands.¹² A modified polyacrylamide resin was fed to rats at 500, 2,000, and 10,000 ppm in their diets for two years without any significant adverse effects, while a similar study with dogs fed 500, 2,000, and 10,000 ppm showed only questionable findings at the 1% level.¹³ Polyfluorotetraethylene (PTFE, marketed as Teflon®) was found to have no adverse effects on weanling rats at 25% levels in their diet for 90 days.¹⁴ Epoxy resins as 1% of a rat's diet for 26 weeks produced no abnormalities, but there was some weight loss. The low oral toxicity of many of these materials may be due to poor gastrointestinal absorption.⁷

Polyurethanes are another group of plastics whose toxicity is low but whose reactants have undesirable properties. Polyurethanes are basically the product of a reaction between a diisocyanate and a polyol. A catalyst, a blowing agent, and a catalyst accelerator are frequently used in the reaction. The most hazardous material used in the reaction is usually the diisocyanate. A commonly used one is toluene diisocyanate (TDI). This is a strong skin and respiratory irritant, and sensitivity reactions with asthma-like symptoms along with severe respiratory embarrassment have been produced by it.¹⁵ This is primarily a hazard in the manufacture of the polyurethane or in *in situ* foaming applications of the finished product. However, residual TDI may be present in the foam product and can present a definite potential hazard. If p,p'-diphenylmethane diisocyanate (MDI) is used as the isocyanate rather than TDI, sensitivity reactions can also develop.¹⁶

Most plastics are not thought of as presenting an inhalation hazard in their finished states, with the exception of such materials as the polyurethanes just discussed. One material which does present a potential respiratory hazard is PVP when it is used in an aerosol form. However, several studies have shown that in actual use this has not caused any significant damage. Lowmsma et al¹⁷ exposed rats to PVP aerosols for eight hours a day, five days a week, for a total of 30 exposures to average concentrations of 118 to 146 mg/cu m with particle sizes ranging between 0.5 to 4 μ . No inflammatory pulmonary response occurred, although there was some lymphoid hyperplasia and parenchymal hyperplasia. In another study using PVP-based hair lacquer sprays, no abnormal x-rays were seen in a large number of hairdressers to suggest the presence of thesaurosis.¹⁸ While another report did document the presence of thesaurosis in hairdressers, attempts to demonstrate the presence of PVP in the lungs were unsuccessful, as have been other attempts to reproduce this disease in experimental animals.^{19, 20}

Another potential hazard is that of pneumoconiosis from inhalation of plastic dusts. One case of pneumoconiosis caused by the inhalation of PVC dust has been reported.²¹ Other work on the respiratory deposition of polystyrene aerosols in man has also been reported. Aerosols of 0.188 μ , 0.557 μ , and 1.305 μ were generated and inhaled by human subjects. The effects of such parameters as respiratory rate, tidal volume, and respiratory flow rates on deposition were discussed. Lower respiratory rates increased deposition, especially of the 1.305 μ particles, but tidal volume and flow rates did not affect deposition.²²

Although the majority of the pure polymers used in making plastics have a low order of toxicity, the finished product may have a significantly higher degree of toxicity. This may be due to several factors. These include residual unreacted starting materials having their own individual toxic hazards; compounds added to the plastics including additives, stabilizers, and plasticizers; and direct hazards encountered in working with the material.

A good example of a plastic containing hazardous unreacted materials is seen with polyurethane foams which may contain TDI. The same is applicable to other plastics where unreacted materials remain in the finished product. A second source of toxic hazards is from plasticizers, stabilizers, and other additives, including hardeners in the plastic. Specific examples include the toxic tricresyl phosphate plasticizers and the less toxic phthalic acid derivatives. Stabilizers include lead salts, cadmium, and tin compounds.²³ Again, it is not within the scope of this paper to discuss the toxicity of individual materials but rather to point out representative examples. A more detailed analysis of certain specific problems will be presented in the section on the toxicity of plastics in medicine. Several good reviews on hazards in manufacturing and using plastics are presented by Harris,²⁴ Zapp,²⁵ Wilson and McCormick,²⁵ Zielhuis,²⁶ and Malten and Zielhuis.⁴ Further references are provided in the well-documented bibliography of Molzon.²⁷ A good review on the toxicity of plasticizers, stabilizers, and various additives was published by Guess and Haberman,²⁸ who also evaluated a number of specific compounds. Of the phthalate plasticizers tested, ten showed no toxic characteristics, while seven others showed some toxicity. None of the five sebacates tested were toxic. Citrate

esters were also relatively nontoxic. Of the stabilizers evaluated, all eleven organotin compounds showed some degree of toxicity. Barium, cadmium, and zinc compounds used as stabilizers were also studied. All of the compounds with cadmium or barium were toxic to some degree. However, the zinc compounds, and particularly those in combination with calcium or magnesium, were either nontoxic or far less toxic than the cadmium- or barium-containing compounds.

Dermatitis

Many of the dermatological problems caused by plastics occur in the curing or hardening process. This is especially true for several of the thermosetting resins, notably the phenolics, amines, epoxies, and polyesters where very little dermatitis is caused by the end product itself. Dermatitis associated with the manufacturing process is usually caused by the previously mentioned agents: monomers, low molecular weight polymers, condensate compounds, fillers, and additives such as cross-linking agents, catalysts, accelerators, plasticizers, and solvents.²⁹ In this section several specific problems which have been encountered will be reviewed.

Formaldehyde resins were reported to have caused a contact dermatitis in several cases. Three dermatological clinical syndromes due to urea-formaldehyde resins have been noted.³⁰ These are (1) the sudden development of an acute eczematous reaction, frequently with periorbital edema; (2) a reaction which starts as a typical eczema, affecting the interdigital areas and backs of the hands and forearms, which may appear after years of contact with the resin without any previous reaction; (3) a combination of both the primary and delayed hypersensitivity reactions. Two common uses of formaldehyde resins are in facial tissue products where they are used to impart wet strength and in textile finishes. In one paper, facial tissues impregnated with a urea-formaldehyde resin were found capable of inducing sensitization reactions in about 6% of the group studied.³¹

In textiles treated with formaldehyde resins to improve crease and shrink resistance a number of cases of contact dermatitis have occurred. One report described patients with a contact dermatitis who had a positive patch test to a 1% phenol-formaldehyde resin without a concurrent sensitivity to formaldehyde. Furthermore, heating the resin for five minutes at 191 to 205°C all but destroyed its reactivity.³² Similar results have been reported by others.^{33, 34}

A distinct problem with contact dermatitis has occurred in plastics containing tricresyl phosphates. One case report attributed a woman's allergic reactions to PVC and cellulose acetate to the tricresyl and triphenyl phosphate plasticizers used in their formulations. This was confirmed by patch testing.³⁵ Another case of contact dermatitis was caused by Saran Wrap[®], a copolymer of vinylidene chloride and vinyl chloride. This, too, was confirmed by positive patch tests.³⁶

Nylon is another plastic which has caused dermatitis reactions. Originally many of the nylon dermatoses reported were due to either the finishes on the nylon or the dyes used. However, there have been reports of dermatitis due to virgin nylon. In one study six cases with positive patch tests to virgin nylon (unspecified type) were described.³⁷

Epoxy resins are a prevalent source of dermatitis. As in the case of other dermatoses the reaction to the epoxy resins may

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be considered as being of two basic types: (1) a toxic or primary irritant due to direct epidermal damage; (2) an allergic type of hypersensitivity reaction. Also, chronic irritation may lead to a chronic eczematous dermatitis which can persist without continuing exposure.³⁸ Epoxy resins may be divided into two types on the basis of their curing process. There are both cold-cured and heat-cured resins and, according to Bourne et al, the dermatological hazard is greater with the cold-cured resins.³⁹ The hazards from cold-setting resins have been reviewed by Grandjean in several factories.⁴⁰ Clinically, the hands, forearms, and head and neck were the areas most frequently affected, with the eyelids and face usually showing more involvement than the forearms and hands. The genitalia were also frequently involved from finger contact.³⁸⁻⁴¹ The areas affected showed an erythema which was usually followed by swelling and erythroedema, and were often dotted with vesicles and blebs. Severe itching was usually absent.⁴² A case of allergic rhinitis has been reported,⁴³ and fingernail bed involvement may lead to the development of paronychia.³⁹ Most of the problems listed occurred from the di- or triamine curing agents used. The lower molecular weight resins also may have some irritating properties, but the higher molecular weight uncured resins and all of the completely cured resins generally may be handled without any dermatological effects.⁴⁴ With regard to the amines, the primary and secondary amines are more irritating than tertiary amines, and the aliphatic groups are more irritating than the aromatics.⁴⁵ Methods of handling various agents and controlling these problems have been reviewed by many, including Bourne⁴⁶ and Calnan.³⁸ Controls include such measures as clothing, gloves, washing, and ventilation.

Spandex, a polyurethane elastomer, has been an important cause of contact dermatitis from clothing. First reported, according to Porter,⁴⁷ by D. Munro-Ashman in 1965, numerous cases have been noted since then. Spandex is used extensively in brassieres and girdles, and the contact dermatitis which resulted has been primarily localized to the skin in these areas. The reaction appears initially as an acute erythema, which may be followed by scaling and sometimes by pigmentation.⁴⁸ In a number of cases it was noted that patients also exhibited sensitivity to rubber and other elastic threads. This in turn led to a search for an agent common to both materials. Mercaptobenzothiazole (MBT), a rubber accelerator, was identified in both materials, and patients who were allergic to Spandex were noted to have positive MBT patch tests. By changing clothing to brands of Spandex not containing MBT the dermatitis was usually prevented.⁴⁹⁻⁵¹ However, Carr has reported cases of contact dermatitis in nine women due to Lycra, a Spandex product not previously associated with contact dermatitis.⁵² None of the patients had a positive patch test to MBT.

Acro-osteolysis

Acro-osteolysis is a new and unique occupational disease associated with manufacturing polyvinyl chloride (PVC). It has not been seen with any other plastics. After an early, tentative case report in 1963, a large number of cases were reported.⁵³ Marin et al described five cases of acro-osteolysis in French workers in 1967⁵⁴ and shortly afterwards Wilson et al reported 31 cases of acro-osteolysis.⁵⁵ The disease in both reports involved only the hands. These and other authors have described

a syndrome characterized by the initial development of Raynaud-like phenomena (intermittent pallor of the extremities, especially of the fingers and toes, brought on by cold or emotion). This was later followed by distal phalangeal osteolysis.⁵³⁻⁵⁶

Clinically, the onset of the disease is usually first signaled by complaints consistent with a Raynaud-like phenomenon, which is often the only finding. In addition, nonspecific complaints of tingling, aching, stiffness, or numbness of the fingers may appear with increasing time. Radiographic findings frequently take a year or more to develop and may be associated with fingertip tenderness. The initial radiographic abnormality is usually a marginal defect of one or more of the tufts of the distal phalanges. With the passage of time the defect develops into a fracture line through the distal phalangeal tuft. The fracture line may then progressively widen as the tuft becomes more separated from the remaining shaft. This has progressed in some cases to the point where the bony tuft disappears, leaving only the shaft of the distal phalanx.⁵⁷

Several features are common among these reports. The only workers affected were those involved in hand-cleaning the PVC polymerization autoclaves. No other factory workers mentioned in these or any other reports suffered risks of this disease.⁵⁸ Other production facilities which cleaned the reactors chemically or by jet water streams, rather than having them scraped manually, did not report the development of this disease. In most reports the osteolysis was confined only to the terminal phalanges of the hand. However, some authors found evidence of osteolytic changes in the sacroiliac joints⁵⁹ and portions of the patella.⁵⁷ Osteolytic changes have also been reported in the phalanges of the feet.⁵⁹⁻⁶⁰

No specific etiological agent for acro-osteolysis has been identified. To evaluate the role of vinyl chloride monomer, Viola exposed rats to levels of 30,000 ppm vinyl chloride for 4 hours per day, 5 days a week, for 12 months.⁶¹ The small metatarsal bones showed periosteal proliferation of cartilage-like material, while bone and connective tissue changes similar to those in acro-osteolysis were observed. While such results are interesting, they do not establish vinyl chloride as being the causative agent in acro-osteolysis. Other speculation on tentative etiologies include a combination of physical insult and an unidentified chemical toxicity. It has also been pointed out that a predisposition of the workers to circulatory disease and local microtrauma may be important.⁵⁶ In a recent review Dinman, Cook, Dodson et al restudied the problem, confirming that only workers who hand-cleaned the reactors were at risk. Again no causative agents could be identified.⁶²⁻⁶⁴

Thermal Decomposition

Hazards from the thermal decomposition of plastics are variable and depend on the particular plastic involved. In general, hazards include flammability, the evolution of both combustible and noncombustible gases, and smoke and particulate formation. Nitrocellulose, one of the oldest known plastics, is extremely flammable, and x-ray film made from it was responsible for a fire in a Cleveland clinic in 1929 which killed 125 persons. Combustion products of the nitrocellulose included carbon monoxide, nitrogen dioxide, and nitrogen tetroxide.⁶⁵

Other plastics may decompose directly when exposed to

heat. For example, phenolic resins are relatively inert but are decomposed by heat to yield products including phenol and formaldehyde.⁶⁶ Melamine-formaldehyde and urea-formaldehyde begin to decompose after 30 minutes at temperatures above 350F with the release of formaldehyde vapors.⁶⁷ Stankevich and Ivanova studied amino plastics and found that the decomposition products which formed were directly related to temperature.⁶⁸ At 130 to 200C aldehydes and hydrogen cyanide (HCN) were formed, while at 250 to 270C carbon monoxide (CO) was also formed. The amount of the compounds formed increased with higher temperatures.

The decomposition products of polyvinyl chloride (PVC) were also found to be a function of temperature. Gaseous hydrogen chloride was released from PVC when the temperature reached about 450F. The rate of release depended upon the temperature and density of the material. Above 650F carbonaceous degradation occurs.⁶⁹ Hydrogen, methane, ethylene, ethane, benzene, and toluene have also been reported as PVC decomposition products at temperatures between 350 to 850C. Furthermore, the same decomposition products were found in both air and helium atmospheres, indicating the importance of temperature rather than oxygen during thermal decomposition.⁷⁰ Cornish and Abar⁷¹ studied the toxicity of pyrolysis products of vinyl plastics in rats. Subjecting rats to decomposition products of 1 to 2 grams of PVC at temperatures up to 550C for up to two hours resulted in death for about 50% of the animals. Death was attributed primarily to CO (maximum concentrations were in excess of 3,000 ppm). However, when death from CO was prevented by adding oxygen to their air stream, pulmonary edema and interstitial hemorrhage developed.⁷¹

Thermal decomposition studies were also done on Acrilan (an acrylonitrile), Orlon (an acrylic product), and related fibers. One author reports that while heating these polymers to 200 to 320C either in air or nitrogen, 2.3% ammonia and 1.3 to 1.4% HCN were released in the pyrolysis products.⁷² Hara and Matsumura⁷³ found that below 400C no HCN was formed from melamine, polyamides, or polyurethane. However, HCN began forming from urea resins and cyanoacrylates above 325C and 375C, respectively.

A summary of the thermal decomposition products from these and various other plastics is listed in a table presented in a Michigan Occupational Health Bulletin.⁷⁴

Polyethylene, too, has been studied during thermal decomposition. Pyrolysis products which formed during the thermocutting and sealing of polyethylene tubes included formaldehyde and acrolein.⁷⁵

Polytetrafluoroethylene (PTFE, Teflon®) presents an unusual and unique thermal decomposition hazard which has been called Polymer-Fume Fever. D. K. Harris,⁷⁶ one of the first to call attention to this problem, reviewed several of the early case histories of workers exposed to PTFE decomposition fumes. The presenting clinical symptoms were discussed and, as noted by Harris, there was always a latent interval between exposure to the fumes of PTFE pyrolysis and the development of symptoms. The first symptom noted was a sense of discomfort in the chest described more as a feeling of retrosternal oppression rather than pain. A dry cough may or may not develop. Systemic symptoms appeared after a few hours with a gradual increase in temperature and pulse rate, followed in most cases by an episode of chills and sweating. The tem-

perature did not exceed 104F. Muscle and joint pains have also been reported,⁷⁷ as well as headaches, nausea, weakness, and shortness of breath.⁷⁸ Recovery takes place fairly rapidly and is usually complete within two days.⁷⁶ The toxicity of the products of pyrolysis have been studied, as well as the conditions under which they form. In one study using rats the 3-hour LC₅₀ was 31.5 gm/hr for pyrolysis at 375C, whereas it was 23.5 gm/hr at 400C.⁷⁹ In another study the principal toxic component was found to be a particulate. This may have had other toxicants absorbed on it.⁸⁰ In one report on the identification of the products of pyrolysis, Coleman et al⁸¹ found that carbonyl fluoride (COF₂) was the principal toxic agent which formed when PTFE was pyrolyzed in air at temperatures between 500 to 650C. Above 650C the major products were carbon tetrafluoride (CF₄) and carbon dioxide. Other fluorocarbons were also found in lesser amounts. Scheel⁸² has confirmed COF₂ as the principal toxic component of pyrolysis at 550C. In other reports, however, the major degradation product at 200 to 400C was the monomer, while above 500C perfluoroisobutylene, a highly toxic compound, was formed.⁸³ Analytical methods for identifying the volatile products of pyrolysis are discussed by Boettner and Weiss.⁸⁴ Although these facts are known about the thermal decomposition of PTFE, the specific agent responsible for polymer-fume fever and the mechanism involved is unknown.

Numerous cases of polymer-fume fever have been reported in several different environments. One report described several cases where all of the men who developed symptoms had handled Teflon®-contaminated material, and all were moderate or heavy smokers. When smoking on the job was forbidden the symptoms ceased.⁸⁵ Other cases of polymer-fume fever which resulted from smoking cigarettes contaminated with PTFE dust have also been noted.⁸⁶ Welti and Hip⁸⁷ have reported that cigarette smoking apparently worsened the effects of PTFE fume exposure. Another source of exposure is through aerosols containing PTFE. Here also contamination of cigarettes was responsible for cases of polymer-fume fever.^{88, 89} One rather unique set of symptoms resembling polymer-fume fever occurred in 39 of 40 persons aboard a C-54 aircraft in flight. Fumes arising from Teflon®-impregnated asbestos tape wrapping on the exhaust manifold of an auxiliary power plant were determined as being responsible for the symptoms.⁹⁰

The hazards of polymer-fume fever are not limited only to the cases previously described. Since PTFE may decompose above 400F,⁸³ environments in which Teflon® is exposed to these temperatures will predispose to this problem. This is especially important in industrial processes in which PTFE may be subjected to grinding and burnishing. To prevent the hazard of polymer-fume fever several general preventive measures should be taken. These include: (1) prohibiting workers from smoking in PTFE-contaminated environments; (2) careful personal hygiene in workers exposed to PTFE products, especially dust, before smoking; (3) elimination of PTFE from environments where thermal decomposition may occur except where essential; (4) ventilation control in environments where PTFE thermal decomposition may occur.

Fillers

Many plastics are compounded with fillers in them to im-

prove their properties and give them additional strength. One widely used filler is fiberglass. Health hazards from fiberglass-reinforced plastics are associated with both their manufacture and use. A good review of manufacturing hazards is presented by Lim et al.⁹¹ One of the chief hazards in using fiberglass-reinforced plastics arises when the material is sawed, ground, burnished, or otherwise handled in such a way that dust is produced. In one study on the pathogenicity of these plastics six substances were evaluated by several routes, including intratracheal, intravenous, and subcutaneous injection. Substances studied were: (1) fiberglass-reinforced polyester plastic with a calcium sulfate (CaSO_4) filler; (2) fiberglass-reinforced polyester plastic with a calcium carbonate (CaCO_3) filler; (3) polyester plastic with a CaCO_3 filler without the fiberglass; (4) fiberglass (pulverized and ball-milled) without the plastic; (5) polyester plastic without either filler or fiberglass reinforcement; and (6) flake glass (pulverized and ball-milled). The fiberglass-reinforced plastics (1 and 2) were described as having the same physical properties as in another report⁹² in which the particle size was less than 10μ . The plastic with the CaCO_3 filler but without the fiberglass reinforcement was prepared in a similar fashion. The particle size of the fiberglass without the plastic or filler varied from 20μ to 70μ . The plastic dust alone (5) was 3μ or less in size, while the flake glass was 1μ to 5μ in size. The data show a moderately high mortality occurred in all groups following intratracheal administration of the samples. Pneumoconiotic lesions were more severe with CaCO_3 than with CaSO_4 containing fiberglass-reinforced plastics. This was also observed for plastics containing CaCO_3 filler but without fiberglass reinforcement. Intratracheal inhalation of fiberglass alone produced only a minimal reaction, but vesicular emphysema was seen in all groups. None of the substances administered subcutaneously caused fibrosis except the fiberglass. Finally, lesions were resolved through phagocytosis of the retained particles.⁹³ In another study done by Schepers,⁹⁴ similar results were obtained.

The effects of fiberglass-reinforced plastics have also been studied with regard to their effects on tuberculosis.⁹⁵ Animals were exposed to fiberglass-reinforced plastic dusts with a CaSO_4 filler at levels of 399 (range 18-775) $\times 10^6$ particles/ft³ for ten months or with a CaCO_3 filler 338 (52-792) $\times 10^6$ particles/ft³ for 24 months. (Particle size was not specified. However, in a similar report⁹² the particle size was less than 10μ .) The tuberculosis infection was intensified in both groups but was more severe in the animals exposed to the sample containing CaCO_3 .

Other work was reported on dust generated in the manufacture of molded automobile body parts made from a fiberglass-reinforced polyester plastic. Again, similar results were reported, and limited pulmonary reactions were produced. The responses obtained were classified as those seen with "inert" dusts.⁹²

Another material which may be used as a filler is asbestos. Here, the hazard of generating dust from sawing or grinding processes is quite significant because of the known pulmonary carcinogenic hazard from asbestos. Precautions taken in handling the various forms of asbestos should probably be used for asbestos-containing plastics.

Plastics in Medicine

Plastics have found widespread use in medicine because of

their strength, inertness, light weight, moldability, and their many available forms. Harris⁹⁶ has reviewed their uses in many areas, including syringes, prostheses, and transfusion apparatus.

Potential hazards from the medical use of plastics arise from: (1) effects of the plastic on the body; and (2) effects of the body in altering the properties of the plastic.⁹⁷ Toxic effects of plastics on the body may be either indirect or direct.

A good example of indirect toxicity from plastics is shown by their interaction with drugs. Several potential problems exist, as outlined by Autian.⁹⁸ These include permeation, leaching, sorption (both adsorption and absorption), chemical reactivity, and alteration in the physical properties of the plastics. Permeation may be a minor or a very serious problem, depending upon the drug involved. For example, if the drug is very sensitive to oxidation the entrance of air (oxygen) into the product through its plastic container may accelerate degradation of the drug. If the gas is carbon dioxide, chemical reaction may lower the pH of the solution and may result in a precipitate forming. Conversely, permeation of the drug out through the plastic container may result in decreased activity.⁹⁹ Leaching is always a potential hazard, and a few examples will be briefly discussed later. Sorption may decrease the activity of a drug. Problems with permeability and sorption make nylon unsuited for storing antibiotics, while polyethylene tubing has been found to absorb small concentrations of steroids and a number of alkaloids according to a review by Autian.¹⁰⁰ Chemical reactivity between a drug and its plastic container is a potential problem. Drugs including adrenalin, apresoline, aqua mephyton, aramine, streptomycin, and terramycin have been found to discolor plastics, although the discoloration was generally due to degradation products rather than the drug itself.¹⁰¹

Direct toxic effects arise with both short- and long-term direct (primarily subcutaneous) tissue contact. Short-term exposure is often a potential source for leaching of materials. Long-term contact has been associated with carcinogenesis, which will be discussed in the last section. Other direct contact hazards include an allergic response to the plastic and problems resulting from processing procedures. One allergic response was seen in persons wearing acrylic dentures. The source of the reaction was later determined as being unreacted monomer remaining in the dentures.⁹⁹

Short-term direct tissue toxicity from various plastics was studied by Lawrence et al.¹⁰² Strips of plastic from 48 different devices, most of which were from vinyl tubing, were implanted through the beveled point of a 15G needle intramuscularly into rabbits and through surgical implantation into rats and mice. Twenty-five of the 48 materials caused a toxic reaction when examined at seven days. Grossly the toxic reaction consisted of encapsulation with a whitish zone around the implant, while histologically multinucleated giant cells as well as polymorphonuclear leukocytes were seen. Analysis by gas chromatography showed that the toxic materials were probably additives in the plastic rather than plasticizers. In a follow-up study several years later Lawrence et al.¹⁰³ studied 50 pieces of currently used plastic tubings, most of which again were vinyl compounds. This time, specimens were studied for seven days in both rabbits and in tissue cultures. Approximately 32% of the tubings studied caused a tissue reaction. Criteria of tissue toxicity again were a whitish

or opaque zone seen grossly around the implant with microscopic evidence of necrosis, eosinophilia, inflammation, giant cells, and fibroendothelial proliferation. Although the toxic components still could not be identified, it appeared that safer additives were being used in the newer tubing, based on the lower incidence of toxic reactions.

Tissue reactivity to nylon, Orlon (a polymerized acrylonitrile), Dacron (a polyester made from polyethylene terephthalate), Teflon® (PTFE), and Marlex® (trade name for a family of olefin polymers) was studied by implantation into the peritoneal cavity of dogs for seven days. Nylon and Orlon both produced numerous adhesions. Dacron produced filmy adhesions, while the Teflon® caused only a few filmy adhesions. However, it should be noted that the Marlex® was used in the form of tiny pellets, while the other plastics were used in the form of the undyed shredded yarn, the pellets being unavailable.¹⁰⁴

Processing of a plastic may also introduce toxic substances into the polymer. This is particularly important where ethylene oxide is used for sterilization of thermolabile plastics. After a brief review of toxic and dermatological problems encountered with ethylene oxide, O'Leary and Guess¹⁰⁵ studied the relationship between the content of the plasticizer di-2-ethylhexylphthalate in a plastic and ethylene oxide sorption. Sorption was found to increase directly as a function of di-2-ethylhexylphthalate content.

Data were also presented on ethylene oxide solubility in dimethyl, dipentyl, and dinonyl phthalate. The toxic effects of ethylene oxide on human erythrocytes was studied, and cell culture studies were done on ethylene oxide sterilized polymers. It was also noted that ethylene oxide can function as a solvent for acrylic plastics such as Lucite and Plexiglas.

Another hazard associated with ethylene oxide sterilization is the formation of ethylene chlorohydrin. As an alternative method to gamma-irradiation for the sterilization of heat sensitive materials, ethylene oxide exposure has been valuable. For example, with PVC tubing ethylene oxide sterilization does not cause the discoloration and decomposition effects seen with irradiation. However, Cunliffe and Wesley¹⁰⁶ consistently found the toxic substance ethylene chlorohydrin (concentration not reported) in physiological saline or anticoagulated blood after these fluids had been exposed to PVC tubing previously sterilized with ethylene oxide. Relatively greater amounts of ethylene chlorohydrin were present if the plastic was preirradiated experimentally before being exposed to ethylene oxide. Washing PVC which had only been irradiated revealed small amounts of chloride. Furthermore, if the plastic sterilized with ethylene oxide alone (without prior irradiation) was then not exposed to a fluid containing chloride ions, no ethylene chlorohydrin formed. On this basis, the authors recommended that PVC tubing sterilized by irradiation should be discarded after use. Plastics sterilized with ethylene oxide should be stored for at least a week before being used because of the hazard of residual ethylene oxide on the plastic.

Analytical methods for the determination of ethylene oxide and ethylene chlorohydrin in plastics and rubber surgical equipment were discussed by Brown.¹⁰⁷

Silicones are a group of plastics which have received much attention for their use in cosmetic and prosthetic devices. One area in which silicones have been used is breast mass augmen-

tation. A number of cases have been reported in which silicone has been injected into the breast with adverse effects. In three such cases reported by Winter et al¹⁰⁸ foreign body granulomata resulted. In the first case a giant cell infiltrate occurred after 18 months. The preparation used was a liquid silicone whose purity was unknown. In the other cases a silicone fluid containing 1% animal and vegetable fats was injected into the breast or mandible. Again, it could not be determined if the reactions were due to the silicone or impurities. In another case report repeated injections of silicone fluid were followed by granulomatous mastitis in two cases. Potential problems include: (1) a local sclerosing granulomatous reaction with permanent scarring; (2) histiocytosis secondary to carriage of silicones from their site of inoculation to regional lymphatic nodes; and (3) possible carcinogenic activity.¹⁰⁹ In a British Industrial Biological Research Association (BIBRA) Bulletin editorial entitled "The Price of Inflation"¹¹⁰ the question of toxicity of silicone fluids for cosmetic injection was discussed. It was noted that, although tumors have been found, a causal relationship has not been proven and that the reactions may be due to contaminants. In discussing the safety of silicone for breast augmentation, Snyderman¹¹¹ advises against using injectable silicone because of its known ability to migrate to regional lymph nodes. Instead, a silicone bag filled with liquid silicone, which could be removed later if necessary, was recommended to increase breast size. A bibliography on the use of silicones in bandages, blood vessels, prostheses, and organs has been prepared by the National Library of Medicine.¹¹²

Plastics have also been used extensively in blood storage bags and in transfusion equipment. Extraction and leaching of toxic substances from the plastic is always a potential hazard. Marcel and Noel¹¹³ reported that blood stored in plastic transfusion bags for 4, 8, 15, and 21 days extracted 4, 7, 11.5, and 11.5 mg% of dihexyl phthalate, respectively. Jaeger and Rubin¹¹⁴ found that blood stored in bags at 4°C for 21 days extracted 5 to 7 mg% of the plasticizer di-2-ethylhexylphthalate (DEHP). Also, patients who received these blood transfusions had DEHP levels of 0.025 mg/gm (dry weight) in their spleens and 0.270 mg/gm (dry weight) in the abdominal wall fat. As the authors state, the phthalate ester plasticizers are generally considered to be of a low order of toxicity. However, this is based primarily on the absence of overt toxic symptoms. Therefore, although such tissue levels are not presently known to be associated with toxic manifestations, further work on "subtle toxicities" may reveal hazards not presently recognized.

Tissue perfusion with plastic tubing has also been used for assessing plastics toxicity. Several effects have been noted. In one report the normal pulmonary response of increased pulmonary vasculature resistance in response to hypoxia was partially abolished when PVC tubing was used to perfuse isolated cats' lungs. Two types of surgical grade plastic tubing were used, both containing the same plasticizer, acetyl-tri-n-butyl citrate in epoxy soya-bean oil. However, different stabilizers were used, and the tubing containing the cadmium-zinc stabilizer appeared less toxic than the plastic with the octyl-tin stabilizer.¹¹⁵

Atkins et al¹¹⁶ evaluated several types of perfusion apparatus using Eagle's minimal essential medium (MEM) as the perfusate, with bone marrow cultures in agar-gel to test for

cytotoxins. Toxic effects were present with polypropylene, plexiglass, and stainless steel apparatus. Specific toxins were not identified. Meyler et al¹¹⁷ used five brands of PVC tubing to perfuse isolated rats' hearts. Three brands of tubing interfered with cardiac function causing negative inotropic effects, arrhythmias, and cardiac arrest. Two brands used caused no immediate deleterious effects. The cardiotoxic effects of the PVC were believed to be a result of the stabilizers used. The organotin stabilizer was very toxic, but the barium-cadmium had no observable toxic effect. Specific compounds, however, were not identified.

One unique hazard from extracorporeal circulation was reported by Lindberg et al.¹¹⁸ Here, ten human patients died following open-heart surgery during which perfusion was maintained with the DeWall extracorporeal pump-oxygenator. At autopsy, clear refractile emboli were seen in capillaries of the brain, heart, and kidney. These were later identified as the same silicone antifoam material which had been used to treat the surface of the oxygenator column and helical debubbling chamber. Identical lesions were produced in the kidneys of dogs perfused on the DeWall pump-oxygenator.

An unusual problem in the use of plastics occurs when they are used as aortic valve replacements. As Little¹¹⁹ notes, arterial blood is a very efficient oxidizing agent and is also a good hydrolyzing agent. Therefore, any plastic which relies on an antioxidant for stability, like polypropylene, is unsuitable for a heart valve.

Leaching may be associated with both short- and long-term hazards. Short-term hazards may occur with prolonged endotracheal intubation for respiratory assistance. The PVC used in endotracheal tubes contains stabilizers which can leach out of the plastic and cause severe irritation after several days of use. Ethylene chlorohydrin may form if the plastic has been sterilized with ethylene oxide, as discussed previously.¹²⁰ Guess and Stetson¹²¹ have reported an increasing incidence of glottic inflammatory reactions after the use of endotracheal tubes. The toxic substance causing the reactions was identified as an organotin stabilizer.

On the basis of these reports, organotin and octyl-tin stabilizers appear to be not only toxic but extractable from plastic tubing. It would therefore appear advisable not to use them as stabilizers in plastics which are to be used for medical application.

Long-term leaching hazards occur when lead-stabilized PVC is used for food packaging and for water pipes. The problem of leaching out PVC stabilizers by water was evaluated for a compound stabilized with 3.77% basic lead phosphite and lubricated with 0.94% basic lead stearate - 0.5 ppm of lead were extracted after 18 months at ambient temperature; no lead was extracted with hard water. On this basis, the plastic was judged as being safe for use in pipes containing flowing water.¹²²

Toxicity standards for plastics have been advocated. In addition to gross parameters for evaluating toxicity by acute and chronic oral feeding studies, Brewer¹²³ has outlined a series of extraction testing procedures and implantation standards for plastics used in medicine. Guess et al¹²⁴ have described other methods for evaluating more subtle forms of toxicity. These include growth in tissue culture, electron and phase microscopy of tissue that has been in contact with the plastic, hemolytic effects, effects on antibody production, and embryonated egg

studies. In the data they presented, the plasticizer dimethyl sebacate killed four of the cell cultures but did not affect the growth of chick embryo cells. Butyl octyl phthalate was found to be innocuous in tissue cultures but did produce egg embryo changes. Rosenbluth et al¹²⁵ also found tissue culture methods to be good indicators of toxicity when a cell monolayer technique was used. A good bibliography on these techniques and methods has been compiled by Molzan.¹²⁶

Plastics and Carcinogenicity

An association between plastic films implanted into animals and subsequent tumor formation was recognized in the early 1940's. Turner,¹²⁷ in 1941, implanted Bakelite discs 18 mm in diameter, 1-1/2 mm thick, subcutaneously into rats. After a period of 18 months or more, four of nine rats developed fibrosarcomas. However, for reasons which were unclear, no tumors formed when pieces of Bakelite 10 mm square, 1-1/2 mm thick, were implanted in mice. Several years later Oppenheimer et al¹²⁸ implanted 2 to 3 cm square pieces of cellophane subcutaneously into one group of rats and wrapped the kidneys of another group with cellophane. After 11 months, 35.7% of the survivors from the first group developed tumors, and 34.8% of the surviving rats whose kidneys were wrapped in cellophane developed tumors. These tumors could be successfully transplanted into other rats. Out of the 23 primary tumors there were 17 fibrosarcomas, 2 liposarcomas, 1 rhabdomyosarcoma, 1 undifferentiated sarcoma, 1 osteogenic sarcoma, and 1 plasmocytoma.

Further work revealed that this tumorigenesis phenomenon was not specific for only a few plastics but occurred with many materials. In a later report Oppenheimer et al¹²⁹ were able to produce malignant tumors in rats and/or mice using cellophane (which had previously been processed in various ways), polyethylene film, a pure polyethylene film, PVC film, Silastic (a silicone product), Teflon®, Dacron, polystyrene, and nylon film. Oppenheimer et al¹³⁰ also demonstrated the carcinogenic potential of metals in rodents. Silver, tin, tantalum, vitallium, and stainless steel foils in the form of circles or squares 1.5 cm wide (thickness not specified) were implanted into male rats. All of the foils except the tin foil induced tumors. These were identified as fibrosarcomas except for one osteogenic sarcoma induced by vitallium. In contrast to the other metals studied, the tin foil was friable and was found in every case to have broken down into a fragmentary mass. This change in physical form may have been responsible for lack of tumor formation. In other work, Oppenheimer et al¹³¹ demonstrated that glass coverslips alone produced tumors in 25% of the rats studied, whereas glass powder alone did not produce tumors even when placed into tissue pockets previously formed with coverslips. Polyethylene powder also induced no tumors except in one questionable case.

Tumor formation has also been produced by other materials. Thick polyvinyl alcohol ("Ivalon") sponges produced sarcomas in 14 of 20 animals.¹³² Polyurethane in sheet, foam, and powdered forms was capable of inducing tumors both by subcutaneous and intraperitoneal administration.¹³³ Stinson¹³⁴ reported that polymethylmethacrylate (Acrylic) and stainless steel discs implanted into guinea pigs produced metaplastic bone changes, while malignancies were produced in rats.

The mechanism responsible for polymer tumorigenesis is un-

clear. Numerous observations have been made, and several theories have been proposed to explain it. One theory suggests that carcinogenesis is due to the physical properties of the implanted film and that it is a nonspecific phenomenon not dependent primarily on chemical interaction between the implant and the tissue. Another suggests that a chemical reaction does indeed occur between the implanted polymer and adjacent tissue which leads to tumor formation.¹³⁵ Data are available which support both theories, and no one explanation of tumorigenesis is currently accepted.

Physical properties are known to be important in tumor formation. As discussed earlier, a film of polyethylene or glass coverslips will produce tumors, but the polyethylene and glass in the powdered form won't. The porosity of the polymer is significant. Brues et al.¹³⁶ reported that tumor production with 0.1 μ pore size filters was comparable with nonporous materials. Pore sizes of 1 μ and larger almost completely prevented tumors, while in the intermediate range (0.1 to 0.45 μ) there was an inverse relationship between pore size and tumor incidence. Goldhaber^{137, 138} reported similar observations. After 18 months Millipore filters of 50 μ and 100 μ were found to cause 60% and 52.9% tumors in mice. When the pore size was increased to 450 μ , only 5% developed tumors.¹³⁷ These results are consistent with the concept of physical carcinogenesis on the basis that films interfere with normal diffusion rates of specific metabolites to or from surrounding cells. Introduction of pores into the film decreases this interference and permits more normal patterns of diffusion.

The influence of a smooth film surface in carcinogenesis has been studied by Bates and Klein.¹³⁹ Using polyethylene discs 20 mm in diameter and 0.015 inches thick, a significantly higher incidence of sarcomas formed in mice that had received discs having a smooth surface than with discs that had a roughened surface.

The theory that polymer tumorigenesis is due to a chemical interaction between the implant and the host has received much attention, and many authors have investigated the biochemical and cellular changes which take place as malignancies occur. Oppenheimer et al.¹⁴⁰ have reviewed several possibilities for the mechanism of carcinogenesis. The question of a low molecular weight impurity acting as the carcinogenic agent was considered. However, since numerous tumors were induced with pure plastics, the primary carcinogen appears to be the macromolecule itself rather than an additive or an impurity. Furthermore, no relationship existed between the number of sarcomas produced and the degree of purity of the film. The lack of carcinogenicity of the monomers styrene, methylmethacrylate, and hexamethylene diamine would indicate that unreacted monomer is not likely to be the active agent for at least these particular polymers. Because plastics were believed to be essentially insoluble in aqueous systems and chemically rather inert, any interaction between them and surrounding tissue was thought to be unlikely. It was also noted that there was no correlation between carcinogenicity and the stiffness or rigidity of the film. However, results of Oppenheimer's work using radioactively tagged molecules, as reported in this paper, show that polymers were in fact degraded and metabolized after implantation in the rat. Although the amount of breakdown was minute and no metabolites were identified, the possibility of chemical carcinogenesis was raised. This could be mediated either through

degradation products or the intermediate production of free radicals. These products in turn could interact with the nucleic acids, or the nucleic acids could be altered by the newly formed reactive centers in the polymer itself.

Several interesting observations have been made by Brand et al.¹⁴¹ In contrast to the rapid and sudden malignant transformation which may occur with a virus, they suggest that polymer tumorigenesis may be regarded as an evolutionary process. Here a chain of premalignant cell generations forms in which there is a gradual selection for more autonomous clones. This is supported by several findings. It is known that after a polymer is implanted in an animal a capsule develops around it. If the film and the capsule are removed within a certain period no tumors develop. Also, if the film alone is removed and the capsule is left in the animal, no tumors develop if this is done before a certain irreversible stage. These observations, and the point at which tumor formation can no longer be prevented by removing the film or film and capsule, are explained by the work reported in this¹⁴¹ and other papers by Brand et al.^{142, 143} They found that two to eight months before the tumor appears premalignant cells have formed. These cells appear to be firmly attached to the film and are not found in the surrounding capsule tissue. Tumorigenic cells then detach from the plastic film and invade the capsule tissue only a few weeks before macroscopic growth of the tumor occurs.

Buon et al.¹⁴⁴ reported similar results. They found that premalignant cells could be transferred along with pieces of film five to six months after initial implantation and up to nine months before the tumor appeared grossly. In addition, cells attached to the film did not undergo normal mitosis, suggesting that malignant transformation and maturation occurred in non-dividing cells. They, too, reported that capsular tissue remained free of premalignant cells until one month before the gross appearance of the tumor.

Johnson et al.¹⁴⁵ studied 49 tumors induced in mice by subcutaneous implantation of plastic films. Histologically, four classes of tumor were present. These were well-differentiated fibrosarcomas, spindle-cell sarcomas, anaplastic round-cell sarcomas without giant cells, and anaplastic sarcomas with giant cells.

Biochemical studies on the capsular tissue have been carried out, and enzyme assays were performed on lactic, malate, and glucose-6-phosphate dehydrogenase activities. These three enzymes had their highest activity one month after polymer implantation and then dropped to lower levels. Nucleic acid concentrations remained constant or decreased slightly. The soluble collagen was highest in the early stages and then decreased significantly, while the insoluble collagen increased with time until a maximum was reached. It then remained constant or decreased slightly.¹⁴⁶

The implications of polymer tumorigenesis are significant from a medical standpoint because the potential carcinogenic hazard from many prostheses is unknown. Plastic sponges have been studied in rats and in human breast implants. Rats which received thin (20 x 20 x 2 mm) implants of "Ivalon" (polyvinyl sponge) developed tumors in 20 months, while those receiving thick implants (20 x 20 x 5 mm) developed tumors after 14 months. Tumors developing from the thick implants were invaded by spindle-cell sarcomas arising from outside the implant. The human breast implants were studied 4 to

18 months after implantation. A foreign body reaction to the implant had occurred with histological inflammatory changes similar to those seen in the rats, but there was no evidence of malignant changes. The possibility was raised, however, that malignant transformation may not have occurred only because the human implants had been in position for too short a time.¹⁴⁷

The carcinogenic potential of intrauterine contraceptive devices (IUD's), many of which are now made from plastic, has received much attention. Southam and Babcock¹⁴⁸ implanted various plastic and steel IUD's, as well as sheets of plastic from which the IUD's were made, subcutaneously into rats. All of the plastic IUD's and some of the plastic sheets contained barium sulfate. None of the rats with stainless steel spiral ring implants developed tumors for periods up to 26 months. All of the plastics studied, including the three types of plastic IUD's currently used, induced fibromas or fibrosarcomas when implanted subcutaneously into rats. However, as the authors state, this does not indicate an oncogenic potential in humans where the IUD's are placed into the uterine cavity rather than imbedded in connective tissue.

Ober¹⁴⁹ studied endometrial changes in 208 women using polyethylene IUD's. After a mean period of 25.1 months, 200 adequate endometrial biopsies were obtained. In 107 biopsies from symptomatic patients (bleeding, pelvic pain, and vaginal discharge), 25.2% showed significant lesions, including diffuse inflammatory changes and atypical glandular hyperplasia with quasi-neoplastic architecture. Minor lesions, including a lymphocytosis, minute foci of granulation tissue, focal disappearance of glands, and endometrial morphology asynchronous by seven days or more from the stated day of the cycle, were seen in 45.8% of the symptomatic patients. In 93 biopsies from asymptomatic patients, 9.7% showed significant lesions, and 50.5% showed minor changes.

Conclusion

Plastics serve many useful and vital functions in a wide number of areas. They are associated with both general and specific hazards in their manufacture and use. A knowledge of these hazards as outlined in this paper is important for control and elimination of these problems in the safe handling of plastics.

References

1. Rose A and Rose E, editors: *The Condensed Chemical Dictionary*, ed 6. New York, Reinhold Publishing Corp, 1961.
2. *Encyclopedia of Chemical Technology*, New York, The Interscience Encyclopedia, Inc. 10:800-818, 1953. Also, Simonds HR and Church JM: *A Concise Guide to Plastics*, ed 2. New York, Reinhold Publishing Corp, 1963.
3. Patty FA, editor: *Industrial Hygiene and Toxicology: Toxicology*, Vol. 2, ed 2 (Rev). New York, Interscience Publishers, 1963, pp. 831-2377.
4. Malten KE and Zielhuis RL: *Industrial Toxicology and Dermatology in the Production and Processing of Plastics*. New York, Elsevier, 1964, 258 pp.
5. McCollister DD et al: Toxicology of acrylamide, *Toxicol Appl Pharmacol* 6:172-181, 1964.
6. Mine CH et al: The toxicology of epoxy resins, *Arch Ind Health* 17:129-144, 1958.
7. Borgstedt HH: The toxic hazards of epoxy resins, *Ind Med Surg* 32:426-429, 1963.
8. Cornish HH and Block WD: The toxicology of uncured epoxy

resins and amine curing agents, *AMA Arch Ind Health* 20:390-398, 1959.

9. Demehl CU: Hazards to health associated with the use of epoxy resins, *J Occup Med* 5:17-21, 1963.
10. Breyse PA: Plastics in automobile body repair shops, *Ind Med Surg* 30:141-144, 1961.
11. Smyth HF Jr and Weil CS: Chronic oral toxicity to rats of a vinyl chloride-vinyl acetate copolymer, *Toxicol Appl Pharmacol* 9:501-504, 1966.
12. Polyvinyl pyrrolidone (PVP) toxicology, *Food Cosmetics Toxicol* 1:212-213, 1963.
13. Christofano EE et al: The toxicology of modified polyacrylamide resin, Paper, Eighth Annual Meeting, Society of Toxicology, Williamsburg, Va, March 10-12, 1969; Abstr. *Toxicol Appl Pharmacol* 14:616, May 1969.
14. Polytetrafluoroethylene toxicology, *Food Cosmetics Toxicol* 1:90-91, 1963.
15. Demehl CU: Health hazards associated with polyurethane foams, *J Occup Med* 8:59-62, 1966.
16. Konzen RB et al: Human response to low concentrations of p,p'-diphenylmethane diisocyanate (MDI), *Amer Ind Hyg Assoc J* 27:121-127, 1966.
17. Lowmsma HB et al: Effects of respired polyvinylpyrrolidone aerosols in rats, *Toxicol Appl Pharmacol* 9:571-582, 1966.
18. McLaughlin AIG and Bidstrup PL: The effects of hair lacquer sprays on the lungs, *Food Cosmetics Toxicol* 1:171-188, 1963.
19. Bergmann M et al: Thesauritis due to inhalation of hair spray, *New England J Med* 266:750-755, 1962.
20. Kinkel HJ and Eder H: Toxicological inhalation studies on the absorption and excretion of resinous basic components of hair spray, *Internat Arch Gewerbepath Gewerbehyg* 22(No. 1):10, 1966; Abstr. *Bull Hyg* 41:1080, 1966.
21. Szende B et al: Pneumoconiosis caused by the inhalation of polyvinylchloride dust, *Med Lavoro* 61:433-436, 1970.
22. Momotani H: The respiratory deposition of polystyrene in aerosols in man, *Japan J Hyg* 21:417, 1967; *APCA Abstr* 13: No. 9463, 1968.
23. Harris DK: Some hazards in the manufacture and use of plastics, *Brit J Ind Med* 16:221-229, 1959.
24. Zapp JA Jr: Toxic and health effects of plastics and resins, *Arch Environ Health* 4:335-346, 1962.
25. Wilson RH and McCormick WE: Plastics. The toxicology of synthetic resins, *AMA Arch Ind Health* 21:536-548, 1960.
26. Zielhuis RL: Systemic toxicity from exposure to epoxy resins, hardeners, and styrene, *J Occup Med* 3:25-29, 1961.
27. Molzon AE: *Plastec Note 5: Health Hazards and Toxicity of Plastics: A Cross-Indexed Bibliography*, Dover, New Jersey, Plastics Tech. Evaluation Center, Picatinny Arsenal, 1962, 20 pp.
28. Guess WL and Haberman S: Toxicity profiles of vinyl and polyolefinic plastics and their additives, *J Biomed Mat Res* 2:313-335, 1968.
29. Key MM: Occupational dermatitis from plastics, *J Med Assoc of Georgia* 57:421-24, 1968.
30. Harris DK: Health problems in the manufacture and use of plastics, *Brit J Ind Med* 10:255-268, 1953.
31. Peck SM and Palitz LL: Sensitization to facial tissues with urea-formaldehyde resin (wet-strength), *JAMA* 160:1226, 1956.
32. Gaul LE: Absence of formaldehyde sensitivity in phenol-formaldehyde resin dermatitis, *J Invest Derm* 48:485, 1967; Abstr. *Bull Hyg* 42:1079, 1967.
33. Berrens L et al: Free formaldehyde in textiles in relation to formalin contact sensitivity, *Brit J Derm* 76:110, 1964; Abstr. *Food Cosmetics Toxicol* 2:622, 1964.
34. Malten KE: Textile-finish contact hypersensitivity, *Arch Derm* 89:215, 1964; Abstr. *Food Cosmetics Toxicol* 2:622, 1964.
35. Pegum IS: Contact dermatitis from plastics containing tri-aryl phosphates, *Brit J Derm* 78:626, 1966; Abstr. *Food Cosmetics Toxicol* 5:830, 1967.
36. Osbourn RA: Contact dermatitis caused by saran wrap, *JAMA* 188:1159, 1964.
37. Morris GE: Nylon dermatitis, *New England J Med* 263:30, 1960.
38. Calnan CD: Dermatitis from epoxy resin systems, *Trans Assoc Ind Med Officers* 13:38-41, 1963.
39. Bourne LB, Milner FM and Alberman KB: Health problems of epoxy resins and amine-curing agents, *Brit J Ind Med* 16:81-97, 1959.

40. Grandjean E: The danger of dermatoses due to cold-setting ethoxylated resins (epoxide resins). *Brit J Ind Med* 14:1-4, 1957
41. Stevenson CJ: Epoxy resin dermatitis. The current position, *Ann Occup Hyg* 8:127-130, 1965
42. Gaul LE: Prevalence of epoxy resin dermatitis, *Arch Derm* 96:227-230, 1967.
43. Morns GE: Allergic rhinitis acquired during the processing of epoxy resins, *Annals of Allergy* 17:74-75, 1959.
44. Birmingham DI: Clinical observations on the cutaneous effects associated with curing epoxy resins, *AMA Arch Ind Health* 19:365-367, 1959.
45. Broughton WE: Epoxy resins in industry. The hazards and their control, *Ann Occup Hyg* 8:131-142, 1965.
46. Bourne LB: Epoxide resins. Epoxide resins and amine catalysts, *Chem & Ind No.* 19:578-579, 1957.
47. Porter PS: Contact dermatitis due to spandex, *Arch Derm* 95:666, 1967
48. Allenby CF et al. Contact dermatitis from spandex yarn, *Brit Med J* 1:674, 1966
49. Fisher AA: Allergenic elements in spandex garments, *JAMA* 201:894, 1967.
50. Joseph HL and Maibach HI: Contact dermatitis from spandex brassieres, *JAMA* 201:880-882, 1967
51. Porter PS and Sommer RG: Contact dermatitis due to spandex, *Arch Derm* 95:43-44, 1967.
52. Carr RD: Spandex dermatitis, *Arch Derm* 96:642-645, 1967.
53. Wilson RH et al: Occupational acroosteolysis: Report of 31 cases, *JAMA* 201:577-581, 1967.
54. Marin A et al: Occupational acro-osteolysis, *Revue de Rhumatisme* 34:340-351, 1967; *Abstr. Occup Safety Health Abstr* 6:373, 1968.
55. Benoit JP: *Occupationally-Induced Acro-osteolysis*, Lyon, France, Imprimerie Bosc Freres, 1967, pp 88; *Abstr. Occup Safety Health Abstr* 6:738, 1968
56. Kovac A et al: Acropathy of the extremities associated with vinyl chloride polymerization—a new occupational disease, *Lijecnicki Vjesnik* 91:5-17, 1969; *Abstr. Occup Safety Health Abstr* 7:427, 1969.
57. Dinman BD et al: Occupational acroosteolysis—a clinical investigation of polyvinyl chloride synthesis workers, *Proceedings, XVI Int'l Congress on Occup Health*, Tokyo, Japan, Sept. 22-27, 1969, pp. 293-296
58. McCord CP: A new occupational disease is born, *J Occup Med* 12:234, 1970.
59. Hams DK and Adams WGF: Acro-osteolysis occurring in men engaged in the polymerization of vinyl chloride, *Brit Med J* 3:712-714, 1967.
60. Cordier JM et al: Acro-osteolysis and associated skin lesions in two workmen employed to clean autoclaves, *Cahiers de Medicine du Travail* 4:1-39, 1966.
61. Viola, PL: Pathology of vinyl chloride, *Med Lavoro* 61:174-180, 1970.
62. Dinman BD et al. Occupational acroosteolysis. I. An epidemiological study, *Arch Environ Health* 22:61-73, 1971.
63. Cook WA et al: Occupational acroosteolysis. II. An industrial hygiene study, *Arch Environ Health* 22:74-82, 1971.
64. Dodson VN et al: Occupational acroosteolysis. III. A clinical study, *Arch Environ Health* 22:83-91, 1971.
65. The hazard of toxic gases from combustion of roentgen-ray films, *JAMA* 92:1764, 1929.
66. Effects of plastic dust, *Brit Med J* 1:42, 1963.
67. Cleary WM: Thermoplastic resins decomposition, *Mich Occup Health* 14:5-6, Spring 1969.
68. Stankevich VV and Ivanova ZV: Toxicity and hygienic standardization of substances formed from the thermal destruction of polymers, *Sb. Prom Toksikol i Klinika Prof Zabolevani Khim Etiol* 1962, p 141-144, *Abstr Chem Abstr* 61:11230e, 1964.
69. Hazardous product produced by electrical insulation, *NBS Technical News Bulletin* 54:54, March 1970.
70. Tsuchiya Y and Sumi K: Thermal decomposition products of polyvinyl chloride, *J Appl Chem* 17:364, 1967; *Abstr Food Cosmetics Toxicol* 7:391, 1969
71. Cornish HH and Abar EL: Toxicity of pyrolysis products of vinyl plastics, *Arch Environ Health* 19:15-21, 1969
72. Lohs KH: The thermal decomposition of polyacrylonitrile fibers into prussic acid as potential source of poisoning, *Zentr Arbeitsmed Arbeitschutz* 14:287, 1964; *Abstr. Chem Abstr* 62:12355e, 1965.
73. Hara N and Matsumura Y: Production of hydrogen cyanide by heating of binders, *Ind Health* 2:208, 1964.
74. A summary of decomposition products, *Mich Occup Health* 7:3, Spring 1962.
75. Hovding G: Occupational dermatitis from pyrolysis products of polythene, *Acta Dermatovenereologica* No. 49:147, 1969; *Abstr. Occup Safety Health Abstr* 8:726, 1970.
76. Hams DK: Polymer-fume fever, *Lancet* 2:1008, 1951.
77. Gualtier M et al: Polymer fever—physiopathological and diagnostic problems, *Archives des Maladies Professionnelles* 31:237-241, 1971; *Abstr. Occup Safety Health Abstr* 9:52, 1971.
78. Robbins JJ and Ware RL: Pulmonary edema from teflon fumes. Report of a case, *New England J Med* 271:360-361, 1964.
79. Birnbaum HA et al. The toxicology of the pyrolysis products of polychlorotrifluoroethylene, *Amer Ind Hyg Assoc J* 29:61-65, 1968.
80. Wantz RS and Kwon BK: The inhalation toxicity of pyrolysis products of polytetrafluoroethylene heated below 500C, *Amer Ind Hyg Assoc J* 29:19-26, 1968.
81. Coleman WE et al: The identification of toxic compounds in the pyrolysis products of polytetrafluoroethylene (PTFE), *Amer Ind Hyg Assoc J* 29:33-40, 1968.
82. Scheel LD et al: The toxicity of polytetrafluoroethylene pyrolysis products—including carbonyl fluoride and a reaction product, silicon tetrafluoride, *Amer Ind Hyg Assoc J* 29:41-48, 1968.
83. Polytetrafluoroethylene toxicology, *Food Cosmetics Toxicol* 1:90-91, 1963.
84. Boettner EA and Weiss B: An analytical system for identifying the volatile pyrolysis products of plastics, *Amer Ind Hyg Assoc J* 28:535-540, 1967.
85. Barnes R and Jones AT: Polymer-fume fever, *Med J Aust* 2:60-61, 1967; *Abstr. JAMA* 201(No. 8):192, 1967.
86. Lewis CE and Kerby GR: An epidemic of polymer-fume fever, *JAMA* 191:375-378, 1965.
87. Welti DW and Hipp MJ: Polymer-fume fever. Possible relationship to smoking, *J Occup Med* 10:667-671, 1968.
88. Bruton DM: Polymer-fume fever, *Brit Med J* 1:757, 1967.
89. "Polymer-fume fever" in Connecticut, *Nat Clearinghouse for Poison Control Centers Bulletin*, Oct. 1961, p. 1-4.
90. Nuttall JB et al: Inflight toxic reactions resulting from fluorocarbon resin pyrolysis, *Aerospace Med* 35:676-683, 1964.
91. Lim I et al: Fiber glass reinforced plastics. Associated occupational health problems, *Arch Environ Health* 20:540-544, 1970.
92. Schepers GWH et al: The biological action of fiberglass-plastic dust (an experimental inhalation study of the dust generated in the manufacture of automobile body parts from a commercial product with a calcium carbonate filler), *AMA Arch Ind Health* 18:34-57, 1958.
93. Schepers GWH: The pathogenicity of glass-reinforced plastics, *Arch Environ Health* 2:620-634, 1961.
94. Schepers GWH: Pulmonary histologic reactions to inhaled fiberglass-plastic dust, *Amer J Pathol* 35:1169-1187, 1959; *Abstr. APCA Abstr* 7: No. 3947, 1961.
95. Schepers GWH: Influence of fiberglass-plastic dust on tuberculosis; an experimental inhalation study of two variables of dust. Histopathologic observations, *Amer Rev Tuberc Pulmonary Dis* 78:512-523, 1958; *Abstr. APCA Abstr* 5: No. 2639, 1959.
96. Hams DK: Medical and surgical applications of plastics, *Chem & Ind* 8:236-242, 1968.
97. Autian J: Toxicological aspects of implants, *J Biomed Mat Res* 1:433-449, 1967.
98. Autian J: Toxicity, untoward reactions, and related considerations in the medical use of plastics, *J Pharm Sci* 53:1289-1301, 1964.
99. Bishop WR and Autian J: *Modern Plastics Encyclopedia* 1970-71, *Toxicology of Plastics in Medicine* 47, No. 10A:8, Oct. 1970.
100. Autian J: Drug packaging in plastics, *Drug & Cosmet Ind* 102:54-62, 154-158, April 1968.
101. Guess WL et al: Drugs which discolored plastics, *Amer J Hosp Pharm* 22:181, 1965.
102. Lawrence WH et al: Toxicity of plastics used in medical practice. I. Investigation of tissue response in animals by certain unit packaged polyvinyl chloride administration devices, *J Pharm Sci* 52:958-963, 1963
103. Lawrence WH et al: Re-evaluation of plastic tubings currently

used in medical and paramedical applications, *J Biomed Mat Res* 3:291-303, 1969.

104. Usher FC and Wallace SA: Tissue reaction to plastics. A comparison of nylon, orlon, dacron, teflon, and marlex, *AMA Arch Surg* 76:997-999, 1958.

105. O'Leary RK and Guess WL: The toxicogenic potential of medical plastics sterilized with ethylene oxide vapors, *J Biomed Mat Res* 2:297-311, 1968.

106. Cunliffe AC and Wesley F: Hazards from plastics sterilized by ethylene oxide, *Brit Med J* 2:575-576, 1967.

107. Brown DJ: Determination of ethylene oxide and ethylene chlorhydrin in plastic and rubber surgical equipment sterilized with ethylene oxide, *J Assoc Off Analyt Chem* 53:263, 1970.

108. Winer LH et al: Tissue reactions to injected silicone liquids, *Arch Derm* 90:588-593, 1964.

109. Symmers WStC: Silicone mastitis in "topless" waitresses and some other varieties of foreign-body mastitis, *Brit Med J* 3:19-22, 1968.

110. The price of inflation, *BIBRA Bull* 7:266, 1968.

111. Snyderman RK: Is injectable silicone safe for breast augmentation? *JAMA* 215:303-304, 1971.

112. Toxicology of Silicone Plastics. Mid-1963 - June 1965. New Bibliographic Series No. S.B. 13-65. Washington, D.C., Bibliographic Services Div., Nat'l Library of Med., 1965, 4 p.

113. Marcel YL and Noel SP: Contamination of blood stored in plastic packs, *Lancet* 1:35-36, 1970.

114. Jaeger RJ and Rubin RJ: Plasticizers from plastic devices: Extraction, metabolism, and accumulation by biological systems, *Science* 170:460-461, 1970.

115. Duke HN and Vane JR: An adverse effect of polyvinylchloride tubing used in extracorporeal circulation, *Lancet* 2:21-23, 1968.

116. Atkins RC et al: Cytotoxins released from plastic perfusion apparatus, *Lancet* 2:1014-1015, 1968.

117. Meyer FL et al: The influence of polyvinyl Chloride (PVC) tubing on the isolated perfused rat's heart, *Circulation Res* 8:44-46, 1960.

118. Lindberg DAB et al: Silicone embolization during clinical and experimental heart surgery employing a bubble oxygenator, *Amer J Pathol* 39:129-144, 1961.

119. Little K: Stricter rules needed for medical plastics, *New Scientist* p. 118-119, 1969.

120. Hazards of prolonged intubation and tracheotomy equipment, *JAMA* 204:624-625, 1968.

121. Guess WL and Stetson JB: Tissue reactions to organotin-stabilized polyvinyl chloride (PVC) catheters, *JAMA* 204:580-584, 1968.

122. Chancellor SF: Toxicity of plastics, *Nature* 185:841, 1960.

123. Brewer JH: Toxicity standards for plastics, *Bull Parenteral Assoc* 19:22-28, 1965.

124. Guess WL et al: Characterization of subtle toxicity of certain plastic components used in manufacture of the polyvinyls, *Amer J Hosp Pharm* 24:495-501, 1967.

125. Rosenbluth SA et al: Tissue culture method for screening toxicity of plastic materials to be used in medical practice, *J Pharm Sci* 54:156-159, 1965.

126. Molzon AE: *Plastic Note 4: Plastics in the Medical Industry: A Cross-Induced Bibliography*. Dover, New Jersey, Plastics Tech.

Evaluation Center, Picatinny Arsenal, 1962, 46 pp.

127. Turner FC: Sarcomas at sites of subcutaneously implanted bakelite disks in rats, *J Nat Cancer Inst* 2:81, 1941.

128. Oppenheimer BS et al: Sarcomas induced in rats by implanting cellophane, *Proc Soc Exptl Biol Med* 67:33-34, 1948.

129. Oppenheimer BS et al: Malignant tumors resulting from embedding plastics in rodents, *Science* 118:305-306, 1953.

130. Oppenheimer BS et al: Carcinogenic effect of metals in rodents, *Cancer Res* 16:439-441, 1956.

131. Oppenheimer ET et al: Observations on the effects of powdered polymer in the carcinogenic process, *Cancer Res* 21:132-134, 1961.

132. Polyvinyl sponge implants and malignancy, *Lancet* 2:653, 1962.

133. Hueper WC: Experimental production of cancer by means of implanted polyurethane plastic, *Amer J Clin Pathol* 34:328-333, 1960.

134. Stinson NE: The tissue reaction induced in rats and guinea-pigs by polymethylmethacrylate (acrylic) and stainless steel, *Brit J Exp Pathol* 45:21, 1964; *Abstr. Food Cosmetics Toxicol* 2:503-504, 1964.

135. Perilous plastics? *Food Cosmetics Toxicol* 3:512-515, 1965.

136. Brues AM et al: Influence of porosity on sarcoma production by subcutaneous implants, *Abstr. Proc Amer Assoc Cancer Res* 10: No. 38, 1969.

137. Goldhaber P: Further observations concerning the carcinogenicity of millipore filters, *Abstr. Proc Am Assoc Cancer Res* 4: No. 96, 1962.

138. Goldhaber P: The influence of pore size on carcinogenicity of subcutaneously implanted millipore filters, *Abstr. Proc Am Assoc Cancer Res* 3: No. 100, 1961.

139. Bates RR and Klein M: Importance of a smooth surface in carcinogenesis by plastic film, *J Nat Cancer Inst* 37:145-152, 1966.

140. Oppenheimer BS et al: Further studies of polymers as carcinogenic agents in animals, *Cancer Res* 15:333-340, 1955.

141. Brand KG et al: Malignant transformation and maturation in nondividing cells during polymer tumorigenesis, *Proc Soc Exptl Biol Med* 124:675-678, 1967.

142. Brand KG et al: Premalignant cells in tumorigenesis induced by plastic film, *Nature* 213:810, 1967.

143. Brand KG et al: Carcinogenesis from polymer implants: New aspects from chromosomal and transplantation studies during premalignancy, *J Nat Cancer Inst* 39:663-679, 1967.

144. Buoen LC et al: Studies on polymer tumorigenesis, *Abstr. Fed Proc* 26:626, 1967.

145. Johnson KH et al: Polymer tumorigenesis: Clonal determination of histopathological characteristics during early preneoplasia; relationships to karyotype, mouse strain, and sex, *J Nat Cancer Inst* 44:785-793, 1970.

146. Danishefsky I et al: Biochemical changes in the connective tissue pocket surrounding subcutaneously imbedded films, *Cancer Res* 27:833-837, 1967.

147. Possible carcinogenicity of plastic sponges, *Brit Med J* 2:1595-1596, 1962.

148. Southam CM and Babcock VI: Induction of subcutaneous tumors in rats by plastic loops and spirals, *Amer J Obst Gynecol* 96:134-139, 1966.

149. Ober WO: Endometrial morphology and polyethylene intrauterine devices, *Obstet Gynecol* 32:782-793, 1968.