# Phthalic Acid Esters: Biological Impact Uncertain

Phthalic acid esters—approximately 1 billion pounds in 1972—are widely used in industry, in the home, and in medical sciences. Most of the phthalates are plasticizers; they can be incorporated into resins, usually polyvinyl chloride (PVC), to impart the desired characteristics of flexibility and workability to these plastics. Until recently the scientific community paid little attention to the rapidly increasing production of phthalates. That situation changed when it was demonstrated that these esters could escape from "inert" PVC plastics. Special concern has been expressed about the potential risk to medical patients who undergo treatment with equipment containing PVC plastics, but there is also evidence that the phthalates have become general environmental contaminants.

The National Institute of Environmental Health Sciences, located in Research Triangle Park, North Carolina, sponsored a conference (*1*) in early September to assess the current state of knowledge concerning the phthalic acid esters. The participants discussed topics that ranged from the objectionable characteristics of phthalates in unmanned space vehicles (they vaporize under flight conditions and interfere with systems and experiments that depend on ultraviolet optical equipment) to their distribution in the biosphere and their possible effects on human health.

The phthalic acid ester most commonly used as a plasticizer is di-2-ethylhexyl phthalate (DEHP). (DEHP is frequently—and erroneously—called dioctyl phthalate.) Other esters of orthophthalic acid are also used, alone or in combination, in plastic formulations. The plasticizers may account for as much as 40 percent of the final weight of the material. None of the esters are chemically bonded to the polymer matrix, but instead they are interspersed between adjacent PVC chains where they essentially act as lubricants. The ability of the phthalates to migrate out of the plastic may have been underestimated because of their low solubilities in water and their low volatilities.

Plasticized PVC's are versatile and inexpensive; they have been extensively utilized in the construction and housing industries; in the home for wall coverings, upholstery, and appliances; in the transportation industry, particularly for the interiors of automobiles and other vehicles; for medical products, including blood bags for transfusions, and for tubing in heart-lung and kidney machines; for food wrappings; and for apparel. Phthalates may also be used as carriers in pesticide preparations, in cosmetics and perfumes, in industrial oils, and in insect repellants.

### Environmental Pollutants

Since the phthalic acid esters are ubiquitous in their distribution, it is not surprising that they are being identified as water and air pollutants. Ronald Hites of the Massachusetts Institute of Technology found phthalate concentrations of 1 to 2 parts per billion in the Charles and Merrimack rivers in Boston. According to Eugene Corcoran of the University of Miami, samples of water taken in 1970 from the northeast part of the Gulf of Mexico, the Mississippi River delta, and the Mississippi River all contained phthalic acid esters. He detected concentrations of DEHP as high as 0.6 part per million in the Mississippi. Gordon Thomas of the Ontario Research Foundation in Canada also found phthalates in air samples.

Little quantitative information is available on the origins of these environmental phthalates. Pesticides that contain phthalate carriers may release them directly into air, soil, and water; volatilization and leaching of plasticizers from PVC is another source of undetermined magnitude. In addition, some bacteria, fungi, and plants have the ability to synthesize phthalates. The extent of biosynthesis by such organisms has not been assessed but most scientists at the conference thought it unlikely that such biosynthesis could be the sole source of environmental phthalates.

The biological significance of the phthalic acid esters in the environment is uncertain. A few scientists apparently believe that the phthalates are relatively biodegradable, at least in comparison to DDT and the polychlorinated biphenyls but most consider that the evidence for biodegradability is still inconclusive. In one experiment, described by Paul Graham of Monsanto Chemical Company, an "activated sludge" of microorganisms, similar to those found in sewage treatment plants, eliminated more than 90 percent of the esters within 48 hours. This experiment was performed under laboratory conditions that may not be comparable to those found in the field.

David Stalling, Foster Mayer, and their colleagues at the Fish-Pesticide Research Laboratory in Columbia, Missouri, are studying the occurrence and toxicology of phthalic acid esters in aquatic organisms. They reported that specimens of fish, crustaceans, and water collected throughout North America contained di-*n*-butyl phthalate (DNBP) and DEHP. They also showed that the species studied could concentrate DNBP and DEHP from water containing quantities comparable to those found in the Charles River; for example, after 7 days the phthalate concentrations of the organisms varied from 350 to 3900 times that in the water. These data imply that DNBP and DEHP can accumulate in the food chain.

According to Stalling and Mayer, the toxicity of DNBP and DEHP to several fish species, including fathead minnows, channel catfish, and rainbow trout, and to a crustacean (crayfish) was low during 96 hours of exposure; however, DEHP inhibited the reproduction of the waterflea, *Daphnia magna*, increased the percentage of abortions in guppies, and significantly reduced the survival of the fry of zebra fish. These investigators have hypothesized that DEHP may affect calcium metabolism because all of the dying zebra fish that had been exposed to the phthalate died in tetany—a symptom that is frequently indicative of a disturbance in calcium metabolism—whereas tetany was not observed in any of the control animals.

The evidence that phthalates can become environmental contaminants and thus exert deleterious effects on some invertebrate and fish species raises the question of whether they are detrimental to human health. All investigators concede that single doses of the phthalic acid esters are not very toxic whether administered orally, by intraperitoneal or intravenous injection, or applied to the skin. Moreover, diets that contained DEHP and were fed to rats, guinea pigs and dogs for extended periods did not produce significant alterations in such gross characteristics as mortality, life expectancy, body weight, and food consumption, except at the higher doses. According to a spokesman for the Food and Drug Administration, no toxicological hazard is associated with the

levels of phthalates that may occur in foods as a result of their authorized use in food packaging. Most current research is directed toward the elucidation of the more "subtle" effects that could result from continuous exposure to very low concentrations of phthalates, the determination of the metabolic fate of esters that do enter mammalian systems, and the delineation of the special hazards that may be suffered by individuals who could be exposed to higher concentrations of phthalates as a result of such medical treatment as blood transfusions.

Several investigators have reported that blood and blood components can leach phthalate plasticizers from plastic blood bags and medical tubing. Robert Rubin, of Johns Hopkins University, and Rudolph Jaeger, now of Harvard University, observed that blood that had been stored in PVC plastic blood bags for 21 days at 4°C contained from 5 to 7.5 milligrams of DEHP per 100 milliliters of blood. Fresh blood that did not contain DEHP acquired similar quantities of the ester when it was circulated through the PVC tubing of a heart-lung or kidney machine. Human platelet preparations that were stored in plastic containers showed even higher concentrations, the amounts ranging from 15 to 20 milligrams per 100 milliliters of platelet concentrate.

Jaeger and Rubin have detected DEHP in the tissues, usually in the lungs of some, but not all, patients who had been transfused or had undergone surgery for cardiac-pulmonary bypass, but they point out that there is no documented evidence of harmful effects induced in such patients by phthalates. They have also found phthalic acid derivatives in the urines of normal individuals. Although these phthalates may have been acquired from environmental exposure, the possibility of biosynthesis cannot now be eliminated.

Darius Jal Nazir, of Hamilton General Hospital in Hamilton, Ontario, and P. P. Nair, at the Sinai Hospital of Baltimore, reported high concentrations of DEHP (13.5 milligrams per 100 grams of muscle) in the lipid fractions of beef heart mitochondria. They also detected lower concentrations in the mitochondria of rabbit, rat, and dog heart muscle. When Michael Stein, also at Sinai Hospital, and Nair investigated the effects of dietary DEHP on lipid metabolism in the rat, they found that DEHP was deposited in the heart and the epididymal fat pad, but not in the liver. Nevertheless DEHP increased both the lipid accumulation in the liver and the total liver weight. Thus, DEHP appears to alter some aspects of metabolism in the rat, although the mechanism of the change is not clear.

### Phthalate Metabolism

Despite its importance, the metabolic fate of the phthalates in mammalian organisms is, for the most part, unknown. Carl Schulz, working in Rubin's laboratory at Johns Hopkins, has studied the metabolism of DEHP administered to rats both intravenously and by stomach tube. In both experiments, metabolism and excretion were rapid. Ninety percent of the intravenously injected DEHP was disposed of by the animal within 24 hours. The metabolism of the DEHP that had been administered by stomach tube was so fast that negligible quantities were found in the tissues. In these experiments, the water-soluble products that appeared in the urine and feces could not be identified as the products of simple ester hydrolysis to phthalic acid and the appropriate alcohol. This is significant because both of these compounds are more toxic than the ester.

According to the data of Elwood Dillingham and M. Pesh-Iman, of the University of Tennessee Medical Units at Memphis, the excretion of DEHP that had been administered to mice was relatively rapid but was not as fast as that observed by Schulz. Several days after the animals were treated, small quantities of DEHP could still be detected in the lungs, brain, fat, heart, and blood, with the lungs having the largest amounts.

John Autian (*2*), Elwood Dillingham, and their colleagues at the University of Tennessee have also explored the "subtle" effects of the phthalic acid esters, including their teratogenic and mutagenic potentials. All of the eight esters that they injected in relatively large doses ranging from 0.3 to 10.0 milliliters per kilogram of body weight increased the number of dead and resorbed fetuses. In addition, these investigators observed fetal malformations such as absence of tails and eyes, twisted hind legs, and skeletal deformities. In another experiment, large quantities of DEHP and dimethoxyethyl phthalate (DMEP) were administered intraperitoneally to male mice before they were mated with untreated females. The result was a significant reduction both in the number of embryos implanted per pregnancy and in the number of live fetuses per pregnancy. Autian and Dillingham interpreted their findings as being consistent with the hypothesis that DEHP and DMEP produce dominant lethal mutations in mice.

According to Autian and Dillingham, some phthalates are extremely toxic to replicating mouse fibroblasts in cell culture. Dimethyl phthalate and DMEP markedly inhibited the reproduction of such cells. The lower concentrations of DMEP had little effect on the cell population in cultures of nonreplicating fibroblasts. Autian and Dillingham think that the comparative insensitivity of nonreplicating cells is consistent with the finding of low toxicity in vitro, provided that it is correct to assume that in most tissues of the mature animal very few cells are dividing. Embryonic cells and germ cells (the cells that form eggs and sperm), however, do undergo periods of rapid cell division. Therefore, the teratogenicity and mutagenicity of the phthalates may depend on the increased susceptibility of actively dividing cells to the phthalic acid esters.

Rubin and Jaeger, in collaboration with Robert DeHaan, of the Carnegie Institution of Washington in Baltimore, observed that beating chick heart cells in culture stopped beating when exposed to microgram quantities of DEHP and that almost all the cells died within 24 hours.

Most of the participants in the National Institute of Environmental Health Sciences conference on the phthalic acid esters agreed that these chemicals do not appear to pose an imminent threat to human health, although certain individuals, those who receive multiple blood transfusions, for example, may experience higher risks than others. Nevertheless, phthalates are widely distributed in the environment and questions concerning the possible "subtle" effects of persistent exposure to very low concentrations have been raised. In his summary of the conference. Lloyd Tepper of the Food and Drug Administration characterized the current situation as "an etiology looking for a disease." Only time—and more research—will tell whether the disease exists.

—JEAN L. MARX

#### References and Notes


1. The proceedings of this conference will be published in January 1973 in the new journal, *Environmental Health Perspectives*.
2. J. Autian, "Toxicity and health threats of phthalate esters: Review of the literature" (Oak Ridge National Laboratory, Oak Ridge, Tennessee, 1972). This report is available from National Technical Information Service, U.S. Department of Commerce, Springfield, Va.