Phthalic Acid Esters - An Overview

by Lloyd B. Tepper*

In recent years those in the scientific community concerned with environmental and public health have been called upon to consider two categories of previously unsuspected materials characterized by wide distribution and long persistence in the environment: mercury, especially organic mercury, and the chlorinated diphenyls (PCBs). To a significant extent this conference presents again the same types of problems previously posed by mercurials and PCBs. We should note, however, one important difference which suggests that fundamental progress has been made: previously, with respect to mercury and PCBs, serious epidemics of overt disease had arisen which stimulated an intensive search for the respective etiologies; we are today in the clearly preferable position of having an etiology which is searching for a disease.

The matter of phthalic acid esters (PAEs) in the environment has come to our attention through the efforts of inquiring scientists who noted the persistent appearance of an unknown substance in dissimilar media. While we can take no credit from these conscientious observers, it is here in a sense distressing to note that for many years it had been known that plasticizers are extractable from blood bags and tubing and yet this information was not fully exploited or disseminated to parties who might have had an interest in the subject.

We have heard that the annual production of the various phthalic diesters approximates 1 billion pounds. These compounds have a number of uses, the principal ones under consideration being related to the plasticizing of polymerized vinyl chloride (PVC). The spectrum of uses of this material encompasses those with minimal potential for phthalate exposure (floor tiles, cable insulation); those with potential for cutaneous exposure (baby pants, boots); those with potential for internal exposure (food wraps and blood bags); those in which respiratory exposure may be significant (occupational or general atmospheric exposures). It appears that environmental dispersion in samples of air and water may be the rule. Once again we must recognize that the apparent presence or absence of PAEs in any medium is to a major extent a function of our analytical capability to recognize and distinguish this group of compounds and to avoid contamination of the sample in the course of collection or assay.

The environmental dispersion or out-migration of PAEs from PVC is influenced by a variety of factors, some of which are inherent to the specific plasticizer, viz., viscosity, molecular weight, and compatability. Other factors reflect the environment ambient to the compounded polymers, viz., adjacent polymers, solvents, temperature, and convection of recipient media. Evidence has been presented that a seemingly inert piece of PVC is in fact an almost metabolizing entity in which the out-migration of phthalates is influenced by coplasticizers such as polyesters of adipic acid, by the character of contacting liquids such as milk or cleaning solutions, and by the sequence of exposure to various dissimilar liquids.

*Associate Commissioner for Science, U.S. Food and Drug Administration, 5600 Fishers Lane, Rockville, Maryland 20852.

The natural history of environmental PAEs remains to be clarified. Under controlled laboratory conditions, it appears that some 90% is biodegraded in 24 hr by activated sludge (aerobic). On the other hand, we have heard that the concentration which exists in certain bodies of water reflects an absolute amount which approximates the entire domestic production. This discrepancy raises important issues of biodegradability under anaerobic conditions which are typical of many rivers and the question as to whether an equilibrium has been reached in which annual additions to the environmental pool of PAEs are balanced by natural degradation. Of more probable importance is the matter of laboratory contamination which may confuse analytical estimates. Comprehensive studies of PAE out-gassing in aerospace systems have their direct corollaries in out-gassing in the laboratory from floor tiles, gloves, tubing, filter paper, and protective coatings. Unusually meticulous attention to analytical equipment, reagent purity, and laboratory atmospheres is obviously central to accurate assay.

Analytical techniques have reached a high state of sophistication at a commensurate cost. Fortunately, certain types of assays for many PAEs can be accomplished through gas chromatography of a suitably prepared sample. The last word remains to be said in the separation of isomers and in the analysis of diisooctyl and diisodecyl phthalates and similar homologs for which peaks are relatively less well defined. Admonitions with respect to extraneous sources of laboratory contamination and the misinterpretation and misidentification of peaks need reiteration.

The toxicology of PAEs has advanced to a point well beyond that in which one counts up the live ones and the dead ones. In acute oral studies in rats, dogs, and other laboratory animals, LD_{50} values are of the order of 10–20 g/kg for the more commonly used PAE plasticizers. Dialkyl esters with longer chains are relatively less toxic than those with shorter chains. Long-term feeding studies at dietary levels of 60 to several hundred milligrams per kilogram-day have shown no toxicity. The question here, of course, relates to those tests and endpoints selected to demonstrate "no effect."

Acute "subtle toxicity" following intraperitoneal dosing of rodents with DEHP at levels of 250 and 500 mg/kg has been demonstrated. Hexobarbital sleeping times have been prolonged under circumstances which indicate that the PAE is not itself a CNS depressant and that the rate of hexobarbital degradation is not retarded. Consequently, one wonders whether or not the administered PAEs influence the distribution or availability of hexobarbital. Other subtle tests have examined the effects of PAE's on the rat brain, on the clearance of carbon particles by the reticuloendothelial system, on the micro-aggregation of platelets, and on the function of chick myocardial cells in tissue culture. Positive responses in each of these tests, in the myocardial test at concentrations of DEHP as low as 4 μg/ml, point to functional phenomena which clearly merit additional investigation. At this point, we know neither the mechanism responsible nor the active agent, possibly a metabolite. It is also a distinct probability that the chemical peritonitis which follows intraperitoneal injection is relevant to many of the observed responses.

The manner and level of dosing in experimental studies call for more critical appraisal. We are frankly on very unstable ground when we attempt to draw conclusions in various reproductive studies when test animals are given massive intraperitoneal doses of relatively insoluble substances such as the PAEs. While one can take great pains to verify and validate the observations themselves, it is almost impossible to establish the significance of these observations for man. Certain physical mechanisms come into play which are essentially irrelevant to human experience and are in fact misleading. We may anticipate dissimilar toxic phenomena to PAEs dissolved in plasma, bound to albumin, associated with lipoprotein, or transported as particulate microglobules in emulsions. If human applicability is our goal, there is not much to be learned from highly

artificial situations which bring irrelevant mechanisms into play. Certainly it has been shown that there are different kinetics of degradation for PAEs in solution and in emulsions.

The matter of PAEs in banked blood and blood fractions would appear to be a matter of prime interest. The evidence is that platelets, in a manner as yet unestablished, play a special role in the out-migration of PAEs from blood bags. Nevertheless, the platelets themselves do not appear to be functionally harmed by this exposure. The search for other responses to PAEs in banked blood needs to be vigorously encouraged. PAEs administered by this route gain direct access to all organ systems. It is to be expected that the recipient of banked blood may have little capacity to handle environmental insults and that his reserve for dealing with PAEs may be small, if indeed one needs to deal with PAEs.

The optimal plasticizer would obviously be one which does not out-migrate from PVC, and no one can quibble with the position that plasticizers in banked blood are not desirable. The extent of their nondesirability is, of course, a function of their biological properties, which are as yet incompletely defined. While appropriate studies merit prompt initiation, we cannot afford to be stampeded into an unsupported demand for unfamiliar alternative plasticizers or polymer systems. All substitutes will invariably require their own specific toxicological appraisal. Moreover, the suitability of so-called nontoxic polymer systems to blood banking technology will require special scrutiny. The physical integrity of the blood bag and the high degree of reliability of present fabrication technology should not be sacrificed for the supposed advantages of other polymers or plasticizers.

On the other hand, it is clear that industry is called upon to create more permanent plasticizers and to consider other unplasticized polymers and multipolymer laminates which are suitable, especially to blood banking. The argument that an intrinsically more suitable polymer system is not adaptable to production technology needs to be critically examined. While these polymer systems may not be suitable to well established PVC fabrication technology, it is not unreasonable to believe that parallel technologies for fabricating other polymers may be developed. We are aware that costs of materials and fabrication are relevant. The position that cost is not a factor when health is concerned is clearly an oversimplication and possibly simple demagoguery.

Data derived from human experience have been reported. Diethylhexyl phthalate (DEHP) associated with the transfusion of bagged blood into patients is detectable in lung, liver, and spleen. Limited studies of phthalate metabolism following transfusion have been reported. The extent to which PAEs or their metabolites occur in normal human populations remains to be defined. While it is invariably painful for the analyst to retract data previously published, we may find that this move is necessary when unrecognized sources of laboratory or hospital contamination become known or when misinterpreted peaks or chromatographic spots become correctly identified.

Human oral toxicity cannot be judged on the basis of three single doses of 5 or 10 ml of DEHP taken by volunteers or in error. It is apparent that PAEs from food packaging materials do enter the body in conjunction with our normal diet. With a presumed no-effect chronic exposure level of 60 mg/kg in animals, our assumption that man's metabolic capacity is adequate to deal with the current dietary load of PAEs would appear to have support. Orally administered DEHP is metabolized more rapidly than it is absorbed by several animal models. The experiments performed in this area, however, are not definitive, and "no-effect" is largely dependent upon the precise effects for which one is searching. While we need not be critical of the standard approach, we naturally wonder if a more detailed inquiry into human toxicology might be warranted. We further wonder at the extent to which one can generalize to the entire class of PAEs from studies performed upon one or two compounds.

Along the line of human investigations, data based upon industrial hygiene and occupational health studies are conspicuously absent. The Russian report of polyneuritis in workers exposed to phthalate esters requires confirmation. Although PAEs are manufactured in closed systems, there are undoubtedly significant populations working in ester synthesis and polymer compounding which are exposed to measurable atmospheric concentrations of PAEs.

There is evidence that aquatic organisms both concentrate PAEs and demonstrate higher levels of vulnerability than do warm-blooded animals. Disturbances of reproduction and growth of aquatic species have been demonstrated in water containing PAEs at concentrations approximating 3 $\mu g/l$. It is entirely possible, therefore, that current levels of PAEs in certain natural bodies of water are sufficiently high to be injurious to aquatic life. These observations redirect out attention to the suggested biodegradability of PAEs.

It would be our unanimous judgment that this conference has been conducted under most inviting circumstances. For this hospitality and attention to arrangements and logistics we are much indebted to Dr. Rall, his colleagues, and the U.S. taxpayer.

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