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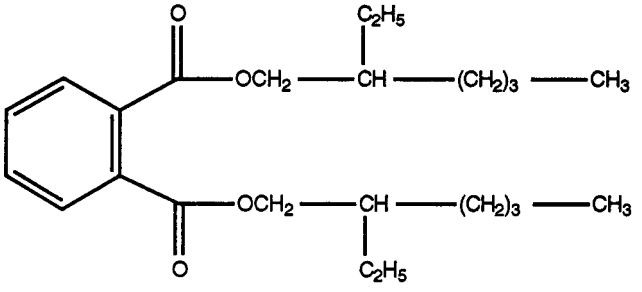
Di-2-ethylhexyl phthalate: A medical concern and a possible marker for chronic fatigue syndrome

Sohail Malik, Margaret A. Kenny and Dedra S. Buchwald

Departments of Laboratory Medicine and Medicine, Chemistry Division, University of Washington, Seattle, WA 98195, USA

Abstract: Di-2-ethylhexyl phthalate (DEHP) is a plasticizer which continuously leaches from some plastics into the environment. It is on EPA's list of carcinogens but there are not extensive data on humans. People who are more in contact with these plastic products are at greater risk of exposure. Hospital patients with high exposure risk were evaluated and their tissues and blood DEHP levels are reported. Elevated DEHP levels were also observed in chronic fatigue syndrome (CFS) patients. A correlation is proposed between metal ions depletion and increased circulating DEHP in CFS patients. It was also found that DEHP cross reacts with some antidigoxin polyclonal antibody preparations. This can lead to false positive results in serum digoxin immunoassays and may indirectly endanger patients on digoxin therapy.

Di-2-ethylhexyl phthalate (DEHP) is today's most widely used plasticizer. More than 500 plasticizers are commercially produced worldwide and DEHP accounts for more than 50% of the total production (1). It is added to plastic to increase its flexibility and processability. The estimated annual production of DEHP is over 1300 million tons. This makes it a substantial threat to humans and environment (2). Being a non-integral component of plastic products, DEHP (Fig.1) constantly leaches into the contacting environment (3). It has been detected in air, water, soil, plants, food, beverages, animals and humans (1). The average DEHP exposure in USA has been estimated to be around 0.3mg/per person per day with maximum 2mg/person per day (4). DEHP is on the US EPA's list of carcinogens. It is hepatocarcinogenic and peroxisome proliferator (5-8). There is sufficient data available for the carcinogenicity of DEHP in mice and rats. However, no adequate data is available to assess the mutagenicity or teratogenicity of DEHP to man (1). The FAO/WHO Expert Committee on Food Additives recommended that the contamination from foods be kept as low as possible in view of the growing global burden of DEHP (9).



In the medical arena three groups of patients are identified as being at greater risk of excessive DEHP exposure. These are patients requiring intra venous (i.v.) infusion of blood products and other solutions (prepared or stored in plastics), the transplant patients whose treatment involves using plastic tubes and i.v. administration sets, and renal failure patients who are on hemodialysis using plastic tubing. In addition to these, the patients who are at higher risk of exposure to plasticizers, are infants, especially the ones who are acutely ill and receiving intensive care. Major excretory organs involved in DEHP metabolism are liver and kidney (10,11). In view of premature size of these organs in infants and insufficient available data on metabolism, their DEHP exposure is of greater concern.

We have selected four groups of patients to survey hospital associated DEHP exposure. Their DEHP levels were evaluated using our recently reported whole blood DEHP assay (12), with suitable modifications. These groups are liver transplant patients, heart transplant patients, non-transplant intensive care patients and infants. The latter survey included autopsy tissue samples from liver, kidney and adipose tissue of babies who died after intensive care. The results (mean values) are summarized in TABLE 1.

TABLE 1 Blood and Tissue DEHP Levels of Selected Hospital Patients and Healthy Donors

Patients	Specimen	DEHP
Healthy donors (n =20)	Blood	0.9 μg/ml
Liver Transplant (n =20)	Blood	3.9 μg/ml
ICU (n =35)	Blood	3.8 μg/ml
Heart Transplant (n =5)	Heart	3.1 μg/g wet
ICU Infants (n =5)	Liver	3.1 μg/g wet
ICU Infants (n =5)	Kidney	2.8 μg/g wet
ICU Infants (n =5)	Adipose	3.3 μg/g wet

Blood of liver transplant patients was also sampled serially during the course of their transplant surgery. They showed increasing blood DEHP values as a function of surgery time. The maximum observation was 19μg/ml. The highest observed blood DEHP level in adult ICU patients was 15μg/ml. Adult heart tissue was obtained from heart removed during the transplant surgery. These specimens had DEHP levels as great as 4.0μg/g wet weight. Lastly, the infant autopsy specimens of liver, kidney and adipose tissues showed DEHP levels upto 8, 7, 8.5μg/g wet weight, respectively. The actual impact of these high body DEHP burdens on acutely ill patients is unknown.

Most recently we investigated the association of DEHP exposure with Chronic Fatigue Immune Dysfunction Syndrome (CFIDS or CFS). CFS is a recently defined, potentially debilitating disease of unknown origin. Patients suffer a constellation of relatively nonspecific symptoms including fatigue, weakness, muscle and joint pain, sore throat, memory loss, difficulty in concentrating, perceived fluctuations in body temperature and depression (13-15). These are nonspecific symptoms associated with many other clinical entities. There are currently no markers for CFS. However there have been some reports about low levels of erythrocyte magnesium in CFS patients (16,17). This was independently confirmed in our laboratory. Concurrently, working with some subjects and controls from the same CFS and control groups, we demonstrated that CFS patients show blood DEHP levels, that were over 5 times greater on average than their matched healthy controls (TABLE 2). We observed abnormal blood DEHP burdens in more than 60% of our CFS patients when compared with the healthy individuals.

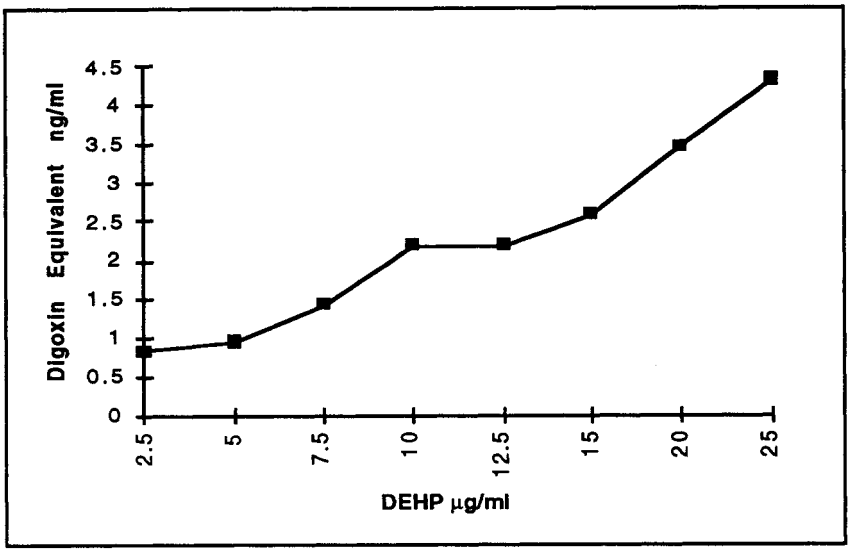
TABLE 2. Blood DEHP Levels of CFS Patients v/s Healthy Controls

Subjects	DEHP Range	Mean
Healthy Controls (n =10)	undetectable - 1.24μg/ml	0.90μg/ml
CFS Patients (n =35)	undetectable - 17.17μg/ml	4.70μg/ml

There are three potential explanations of elevated blood DEHP levels in CFS patients: i) metabolic abnormality (congenital or otherwise), ii) higher DEHP intake iii) combination of both. We are investigating these and can rule out the presence of chronic or acute liver or kidney disease in our CFS study group. We are currently investigating the association of metalloenzymes with DEHP and its metabolites. We believe that increased circulating DEHP causes metal ions depletion in CFS patients. The depletion of metal ions in CFS patients may lower the activity of metal dependent enzymes and this may result in fatigue like symptoms.

Finally, we discovered an indirect hazard of DEHP associated with a widely used laboratory test. Our results indicated that DEHP cross reacts with at least one polyclonal antidigoxin antibody preparation used in a commercial serum digoxin assay kit. Digoxin is one of the most widely used cardiotonic drugs in hospital settings. The cross-reactivity of DEHP with a serum digoxin immunoassay can lead to false positive digoxin measurements. Patients with increased blood DEHP burdens - those who are on hemodialysis and those in ICU are at risk of DEHP interference with the monitoring of their drug therapy. The relationship between digoxin cross-reactivity and DEHP is presented in TABLE-3.

TABLE 3 Dose response curve of DEHP in digoxin free serum, measured by a commercially available digoxin radioimmunoassay kit



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