



AdvaMed

Advanced Medical Technology Association

Backgrounder

PEROXISOME PROLIFERATION

While the world's rat population has good reason to fear a diet of large doses of DEHP, numerous studies have confirmed that patients are unlikely to develop adverse health effects from DEHP-containing medical products. A key factor in understanding the liver tumors observed in rats and mice as a result of oral DEHP exposure is the scientific data explaining "peroxisome proliferation." Peroxisome proliferation is the process in which rodent liver cell compartments react abnormally, eventually leading to cancer in their livers.

Of Mice ...

A 1982 study reported that some rats and mice fed massive doses of DEHP over their lifetimes – a dose more than 100 times greater than the highest levels of human exposure to PVC-containing medical devices – developed liver tumors.ⁱ In susceptible animals, DEHP is the "key" that initiates this process of peroxisome proliferation. When rodents ingest DEHP, a stomach enzyme rapidly converts DEHP to MEHP, which is further broken down in ways different than in humans. These breakdown products, that are unique to susceptible rodents, are thought to cause their peroxisome proliferation and ultimately their liver cancer.^{ii,iii,iv.}

and Men ...

Humans and rodents breakdown and eliminate DEHP very differently. These differences may well explain why some rodents are susceptible to liver cell peroxisome proliferation and ultimately their liver cancer. The breakdown of DEHP in humans does not go through a pathway of "oxidative" metabolism like it does in rodents. The human breakdown products are easily eliminated, and there is no credible evidence that the process of peroxisome proliferation takes place in humans.^{ii,iii,iv.}

and Other Animals ...

Studies have conclusively demonstrated that liver cells in primates, including humans, are not susceptible to peroxisome proliferation when exposed to DEHP.^{ii iii iv.} Additionally, no indications of liver cancer from DEHP exposure were shown in studies of guinea pigs, Syrian hamsters and two strains of rat.^{ii.} Furthermore, in mice genetically altered to eliminate their unique peroxisome-proliferation-response mechanisms, neither peroxisome proliferation nor other adverse liver changes occurred following DEHP exposure.^{v.} Additionally, several studies have conclusively demonstrated that liver cells in primates, including humans, are not susceptible to this cancer-causing mechanism.^{ii iii iv.} A 1996 scientific review of almost 500 studies concluded that liver cancer in humans from DEHP exposure is extremely unlikely.^{ii.}

More conclusions of safety.

The study results are mirrored in real-world experience. If humans were at an increased risk of liver cancer from DEHP exposure from medical products, it would have become apparent after decades of kidney dialysis. Dialysis patients are exposed to PVC and DEHP on a chronic basis, and yet a 1990



report from the Commission of the European Communities shows them to have no increased incidence of liver cancer due to exposure to DEHP.^{vi}

The weight of scientific studies over the last two decades has led the World Health Organization and the Commission of The European Communities to state that there is not sufficient evidence to classify DEHP as a possible or probable human carcinogen.^{vii.viii} Importantly, the World Health Organization's International Agency for Research on Cancer (IARC) recently downgraded its classification of DEHP to the category reserved for chemicals with no evidence of cancer causing potential in humans, saying "the mechanism (peroxisome proliferation) by which DEHP increases the incidence of hepatocellular tumours (*sic*) in rats and mice is not relevant to humans."^{ix} Because of the old rodent studies, DEHP is still listed by the US Environmental Protection Agency (EPA) as a probable human carcinogen. However, the EPA Integrated Risk Information System (IRIS) database indicates that there is inadequate data to establish a causal link between human exposure to DEHP and human cancer.^x In fact, the Director of the Office of Health and Environmental Assessment at EPA, as well as other EPA scientists, have challenged the relevance of the data used to classify DEHP as a probable human carcinogen.^{xi}

April 2000

ⁱ United States National Toxicology Research Center, "Carcinogenesis Bioassay of Di(2-ethylhexyl) Phthalate in F344 Rats and B6C3F1 Mice" (feed study), *Technical Report No. 217*, (Washington DC, 1982).

ⁱⁱ W.W. Huber, B. Grasl-Kraupp, and R. Schulte-Hermann, "Hepatocarcinogenic Potential of Di(2-Ethylhexyl) Phthalate in Rodents and Its Implication on Human Risk," *Critical Reviews in Toxicology*, no. 26(4), (1996), pp. 365-481.

ⁱⁱⁱ Woodyatt, et al, *Carcinogenesis*, vol. 20, no. 3, pp. 369-273 (1999).

^{iv} "Peroxisome Proliferation and Its Role in Carcinogenesis," IARC/WHO Consensus Report, IARC Technical Report No. 24, (Lyon, 1995)

^v J.M Ward, J. M. Peters, C. M. Perella, and F. J. Gonzalez, "Receptor and Nonreceptor-mediated Organ-specific Toxicity of Di(2-ethylhexyl) Phthalate (DEHP) in Peroxisome Proliferator-activated Receptor α -null Mice," *Toxicologic Pathology*, no. 26, (1998), pp. 240-246.

^{vi} *Official Journal of the European Communities* no. C94/8-9, (April 11, 1991).

^{vii} P. Lundberg, J. Hogberg, and P. Garberg, "Environmental Health Criteria 131," Diethylhexyl Phthalate, World Health Organization (Geneva, 1992)

^{viii} C. Ripa di Meana, Commission of the European Communities (EC) Official Journal of the European Commission no. C 94/8 no. 11, (1991), p. 4.

^{ix} IARC monographs on the *Evaluation of Carcinogenic Risks to Humans*. February, 2000. Available at <http://193.51164.11/htdocs/announcements/vol77.htm>.

^x EPA IRIS Database, Di(2-ethylhexyl) Phthalate (DEHP). CASRN 117-81-7, Section II, "Carcinogenicity Assessment for Lifetime Exposure," Subpart A.2, Human Carcinogenicity Data, (February 1, 1993).

^{xi} V.J. Kimm and William H. Farland, US EPA, Letter to K. Olden, US National Toxicological Program, (June 9, 1992).