REVIEW ARTICLE

Di(2-ethylhexyl)phthalate (DEHP)

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Di(2-ethylhexyl) phthalate or DEHP is a colorless, oily liquid and notably, with respect to clinical concerns, is soluble in blood and body fluids containing lipoproteins. Despite being listed as a possible human carcinogen in the 1980's, more recent concerns have focused on its potential toxicity as a result of leaching from medical devices into patients via intravenous or enteral routes. Initial discussion of this problem was reported in the medical literature over 20 years ago. This article provides an update on the status of DEHP as a potential reproductive toxin and the potential implications for high-risk population groups (most notably neonates). The use of the precautionary principle for a guidepost in relating human exposure effects to chemical agents, including DEHP, has become a topic relevant to all health care professionals and is discussed herein.

KEYWORDS: DEHP, MEHP, phthalates

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INTRODUCTION

Di(2-ethylhexyl) phthalate or DEHP is a colorless, oily liquid and notably, with respect to clinical concerns, is soluble in blood and body fluids containing lipoproteins. DEHP was first made in the United States in 1939; production peaked in the 1980's. Approximately 95% of DEHP is used as a plasticizer in polyvinyl chloride (PVC) resins for fabricating flexible vinyl products.[1] PVC resins have been used to manufacture many consumer products, including children's chewtoys.[2] Amazingly, 117,500 metric tons of this product were manufactured in 1994.[1] Historically, DEHP constituted almost 50% of all phthalate ester plasticizers used in this process. This percentage has dropped due to phthalate-related health concerns.[1]

Primary routes of exposure to DEHP are inhalation, ingestion, dermal contact and through a variety of medical procedures.[3] Medical supplies containing PVC include disposable medical examination or surgical gloves, extracorporeal membrane oxygenation (ECMO) circuits, umbilical catheters, nasogastric tubes, intravenous (IV) and blood storage bags, and flexible medical tubing for administering parenteral products (Table 1).[3] Despite being listed as a possible human carcinogen in the 1980's,[1] recent concerns have focused on its potential reproductive toxicity as a result of leaching from medical devices into at-risk patient populations (most notably neonates) via the IV or enteral routes.[4,5]

ABBREVIATIONS: BSP, bromosulfophthalein; cAMP, cyclic AMP; CDC, Centers for Disease Control; FSH, follicle-stimulating hormone; DEHP, Di(2-ethylhexyl) phthalate; ECMO, extracorporeal membrane oxygenation; FDA, Food and Drug Administration; GI, gastrointestinal; IV, intravenous; MEHHP, mono-(2-ethyl-5-hydroxyhexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxohexyl) phthalate; MEHP, monoesters phthalate; NICU, neonatal intensive care unit; NOAEL, no observable adverse effects level; NTP, National Toxicology Program; PVC, polyvinyl chloride; TI, tolerable intake; TPN, total parenteral nutrition

DEHP METABOLISM

Di(2-ethylhexyl) phthalate is metabolized to monoesters phthalate (MEHP), which is the toxic agent implicated in adverse health effects.[6,7] The phthalates are hepatically metabolized via

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Table 1. Commonly Used Medical Products Containing DEHP

Tubing	Catheters
Blood administration sets	IV catheters
Cardiopulmonary bypass circuits	Suction catheters
ECMO circuits	Urinary catheters
Hemo- and peritoneal-dialysis tubing	Umbilical artery catheters
IV infusion sets	**Storage bags**
Nasal cannulae	IV solutions
Respiratory and ventilator tubing	Enteral and parenteral nutriton bags
Endotracheal tubes	**Miscellaneous**
Nasogastric feeding tubes	Exam gloves
Nasojejunal tubes	Syringes

ECMO, extracorporeal membrane oxygenation; IV, intravenous

glucuronidation and are primarily eliminated through urinary excretion. Due to developmental issues these mechanisms of elimination are not developed in healthy infants until the age of 3 months. Likewise, both phthalate elimination routes may be compromised in ill premature infants. The role of the lipase enzyme system on phthalate gastrointestinal (GI) conversion of DEHP to MEHP and subsequent enteral absorption has been documented, more notably in rodents than primates.[6] The possible "anti-protective" effect of breast milk, salivary and gastric lipases in allowing neonatal conversion of DEHP to MEHP was noted in the 2003 American Academy of Pediatrics (AAP) technical report.[7]

Neonates undergoing routine blood transfusions may be exposed to amounts of DEHP (and MEHP) that are 1–2 orders of magnitude above those noted in the general population who are exposed to the same agent.[3] Concentrations of DEHP in necropsy tissues (i.e., heart and GI) from premature infants who received varying quantities of blood products were significantly higher when compared to infants who had not received blood transfusions.[8] Regardless of transfusion history, autopsied tissues from adults exhibited similar DEHP concentrations. The similar findings between adults and infants who received transfusions is attributed to more mature metabolism and excretion of DEHP in the adults.[9] The Food and Drug Administration (FDA) concluded that neonatal DEHP exposure via total parenteral nutrition (TPN), enteral feedings via gavage tubes, exchange transfusion and ECMO exceeds both NOAEL (no observable adverse effects level) and TI (tolerable intake) that has been documented in animal models and corrected for interspecies differences.[10] Medical exposures from simultaneous interventions in the same patients (e.g., ventilation, nasogastric tubes, transfusion, IV administration and TPN) have not been quantified. Such exposures may result in concentrations that are considerably above those documented for single medical procedures.[3]

TOXICITY

Heightened concerns about DEHP exposure occurred as a result of the 2001 Health Canada expert panel report.[11] Environmental action projects of Greenpeace, Healthcare Without Harm and Physicians for Social Responsibility prompted this summary of findings accompanied by recommendations about DEHP. Critically ill infants were felt to have the highest risk for toxicity due to multiple and prolonged exposure to DEHP leaching from PVC-containing medical devices and tubing/bags. Male low-birthweight infants were deemed at special risk as a result of DEHP's potential (via its metabolite, MEHP) to act as a reproductive and developmental toxicant. MEHP causes injury to the Sertoli cells of the testes, thereby functioning as an "endocrine disrupter."[12-15]

Phthalate-induced testicular injury was initially reported in 1982.[16] The U.S. Environmental Protection Agency Science Policy Council took an interim position on the subject in 1998.[17] Further review regarding DEHP and human patients was issued by the National Toxicology Program's (NTP) Center for Evaluation of Risks to Human Reproduction[3] and the FDA via the Center for Devices and Radiological Health,[10] resulting in a formal FDA advisory warning to clinicians in 2002.[18] Additional evidence also implicates DEHP in causing pulmonary and hepatic effects via ECMO, parenteral nutrition and endotracheal tube use.[19-22] The California Enviromental Protection Agency (EPA) listed DEHP as a reproductive toxin under Proposition 65 provisions in October of 2003.[23]

Based on estimated parenteral exposure levels, the Expert Advisory Panel for Health Canada,[11] classified sub-populations as "greatest risk" or "possible but presently undetermined risk" (Table 2). The report further limited its recommendations to IV delivery products, preparatory or storage products. The panel further recommended that actions to remove DEHP from medical devices and

Table 2. Procedures Posing the Highest Risk of Exposure to DEHP

Procedure	At-Risk Group
ECMO	Neonates
Hemodialysis	Peripubertal males Pregnant or lactating women
Nutritional supplementation	Children and adults on enteral nutrition Neonates on TPN
Complex or multiple	Sick neonates requiring multiple procedures Heart transplantation patients Heart bypass patients
Transfusion	Trauma patients requiring massive infusion of blood Neonates undergoing exchange transfusion

*adapted from reference 26

treatments be implemented as soon as possible to protect those sub-populations at greatest risk - fetuses, newborns, infants and young children undergoing high risk procedures. One exception to the recommendations was blood storage bags, which have no non-DEHP alternative at present.

The panel advised that products be labeled as containing DEHP to facilitate use of non-DEHP substitution products if readily available.[11] Along this line, the FDA urged manufacturers to voluntarily label DEHP-containing products in July of 2002.[18] Novation, one of the largest hospital purchasing groups in the United States, recently published a web-based synopsis (Pediatric Clinical Exchange) and a catalog of products listing those that contain DEHP.[24] Healthcare Without Harm provided audit guidelines for health care organizations to use when formulating purchasing decisions regarding PVC-containing devices.[25] California Assembly Bill 1139 (Lowenthal-Long Beach/San Pedro), which would have required product labeling by 2005, failed in committee as a result of lobbying efforts toward California blood banks, which were exempted under provisions of the bill (verbal communication, Physicians for Social Responsibility; Los Angeles). DEHP-containing IV bags and IV and TPN tubing were phased out of use in December 2002 at all four MemorialCare NICUs, including Miller Children's Hospital.[26]

THE EVIDENCE

Select studies are presented below. The NTP Center Report provides the most extensive summary of studies to date for readers interested in more details.

In vivo studies

Loff and colleagues examined the possible relationship between DEHP leaching and hepatobiliary dysfunction using an *in vivo* estimation of exposure to TPN solutions, blood products and medications.[27] The authors concluded that exposure levels were concerning, especially for ill premature neonates.[27] In a second analysis, the same group showed that extraction of DEHP is highly dependent on temperature, contact time and lipophilic content of infusate.[28] In 2001, Kambia et al published a method allowing for the quantification of DEHP in TPN.[29] Mazur demonstrated that lipid-containing formulas stored in PVC bags exhibited DEHP concentrations that increased with both time and temperature.[30] Latini and Avery documented DEHP loss from used and unused endotracheal tubes by multiple analytical methods.[20]

Animal studies

Rhesus monkeys undergoing chronic transfusion with PVC-stored blood products exhibited abnormal liver scans, BSP (bromosulfophthalein) clearance and histopathology compared to controls using polyethelene containers.[31] DEHP exposure was similar to that estimated for pediatric human patients who received chronic transfusion therapy over a 12-month period. The only autopsied animal had significant concentration of DEHP in liver, testes, heart, and omental fat tissue. DEHP and its monoester metabolites caused testicular injury in rat seminiferous tubule cells, similar to that seen in the intact animal.[16] Moore used a Sprague-Dawley rat model and demonstrated dose-related effects on male offspring including reduced anogenital distance, areola and nipple retention, undescended testes, and permanently incomplete preputial separation.[14] An antiandrogenic sensitivity effect was seen early in development with *in utero* and lactational exposure. The author concluded that DEHP may act via unique mechanisms distinct from other antiandrogens.[14]

Lovekamp-Swan's model in rats showed that MEHP acts on ovarian granulosa cells by decreasing FSH-stimulated cAMP stimulation and by activating peroxisome receptors, thereby suppressing estradiol production and leading to anovula-

tion.[32] Large doses of DEHP caused altered milk production/composition in Sprague-Dawley rats in a study by Dostal and others.[33] DEHP/MEHP was shown to be transmitted via the lactating female rat to suckling pups. Multiple doses produced an increase in hepatic peroxisomal enzyme activity.

Human studies

The presence of DEHP/MEHP in cord blood was studied in 84 consecutive newborns in Italy.[34] Findings from this study confirmed that human exposure to DEHP can occur *in utero* and that phthalate exposure may be associated with shorter pregnancy duration. Significantly high concentrations of phthalates and the monoester metabolite were identified in 68% of samples from menstruating females versus case controls in an intriguing paper by Colon et al.[35] The authors felt that premature sexual development in Puerto Rican female children may prove to be an unfortunate example of the impact of endocrine-disrupting environmental chemicals at a critical stage of human development. Hillman and colleagues documented the accumulation of DEHP in neonatal cardiac and gastrointestinal tissues following umbilical catheter placement and blood product administration.[8] Risk factors associated with the presence of plasticizer in neonatal tissues included catheter presence, blood product exposure and exchange transfusion.

The Sjoberg group studied four infants that underwent exchange transfusions.[36] Plasma estimations of DEHP/MEHP in the transfused blood yielded exposure rates of 0.8–3.3 mg of DEHP/kg body weight and 0.05–0.20 mg of MEHP/kg body weight, respectively. Thirty percent of the DEHP exposure was from non-blood bag transfusion set sources (i.e., tubing). Peak DEHP plasma values were as high as 19.6 mcg/mL and were followed by a rapid decline, reflecting tissue distribution. The slow MEHP elimination phase was of concern as MEHP is a toxic metabolic product in animals. The same year, Sjoberg reported DEHP/MEHP pharmacokinetic profiles in six infants that underwent exchange transfusion.[37] Baseline DEHP concentrations increased 10–50 fold with the procedure. MEHP concentrations declined more slowly than did those of DEHP. Because hepatic clearance (i.e., oxidation/glucuronide conjugation) is immature in newborns these patients are less able to eliminate DEHP. Hence, when compared to adults, neonates have persistent exposure, which was noted to be potentially deleterious.

Roth described potential pulmonary toxicities in three premature infants who were mechanically ventilated using PVC respiratory tubing systems.[21] Clinical presentation was similar to that noted with bronchopulmonary disease. Two infants exhibited episodes of respiratory deterioration associated with high concentrations of DEHP extracted from respiratory circuit condensate. Autospsy revealed DEHP in lung tissue from the one infant who expired.

The Centers for Disease Control (CDC) reported the first quantitative assessment of DEHP metabolites in premature infants.[38] Urinary concentrations of MEHP, MEHHP (mono-(2-ethyl-5-hydroxyhexyl) phthalate and MEOHP (mono-(2-ethyl-5-oxohexyl) phthalate were assessed in six premature newborns. Levels of all three DEHP metabolites varied widely. The urinary mean and median concentrations of MEOHP and MEHHP were 1 order of magnitude higher than those for MEHP. The geometric urinary mean concentrations were found to be severalfold higher than in the general United States population.

DISCUSSION

The statement made 25 years ago that "the major components of plasticized PVC have been examined over a span of years and each passing year sees a confirmation of the lack of toxicity" has been proven to be ill-advised.[39] While DEHP does not currently warrant labeling as a human carcinogenic agent[40,41] the evidence against DEHP constitutes a realistic public health threat for high-risk populations. Citing the summary findings of the NTP report[3]—"Based on the morphological, functional and biochemical endpoints, the Sertoli cell is a cellular target for neonatal, pubertal, and adult [DEHP] exposures. Testicular toxicity in the postnatal phase of life resulting from DEHP exposure occurs because of the metabolism, to MEHP, the proximate toxicant." Since the bulk of available data regarding toxic effects of DEHP are extracted from non-human studies, the "evaluation of human reproductive risk must be extrapolated from studies…where species differences in metabolism…are important considerations." Despite gaps in current scientific knowledge, the NTP experts concluded that "the late gestational

and neonatal period…represents a time of potentially high sensitivity to DEHP-induced disruption of the reproductive system" and that "low-dose studies examining sensitive endpoints following late gestational exposure are a critical data need." The American Academy of Pediatrics reviewed this issue and also concluded that "improved understanding of the toxicokinetics of phthalates…in subhuman primates or exposed humans, would enable more accurate evaluation of acceptable exposure levels." They advised further that "[more research]…of the toxicogenetics of phthalates in sensitive populations, including pregnant and lactating women, premature infants, full-term infants, and small children, is also needed.[7]"

Baskin, Himes and Colborn have examined hypospadias, which is one of the most common congenital anomalies in the US (1/250 live male births). They suggest that rather than classifying this lesion as idiopathic-multifactorial in etiology, more specific antiandrogenic mechanisms may need to be proposed, citing the need for new epidemiologic approaches to determine whether endocrine disrupters are involved in the etiology of hypospadias.[15] Interestingly, Hussain et al documented a 10-fold increased incidence of hypospadias in a 13-year survey of two tertiary neonatal intensive care units (NICUs) in Connecticut over the last decade.[42]

Recent editorial comments suggest that the usual dose-effect-toxicity risk model is not sophisticated enough to predict safety for the human species. Developmental risks related to timing of gestational exposure and rate of absorption may be more important than the total quantity of the exposure.[43] The vulnerability of children has become one of the central public health concerns of our times. Prevention of problems in neurologic development and reproduction that stem from early life exposures…are not reparable later.[43] "When an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause-and-effect relationships are not fully established satisfactorily."[44] This "precautionary" principle was cited in the NTP report[3] and was recently reviewed in detail by multiple environmental scientists.[45] Synonyms include the "foresight principle," primary prevention, "first do no harm," and prudent avoidance.[45] Critics of this proactive approach to uncertainty must face a flaw in their reasoning—that the absence of [current] evidence of harm is synonymous with safety.[45]

SUMMARY & CONCLUSIONS

On a patient-by-patient basis, there must be an assessment of the risk vs benefits vs cost-effectiveness analysis regarding DEHP exposure.[7,24] Every effort to reduce the exposure to DEHP, especially in high risk populations, should be undertaken. Hemodialyzed, multiply-transfused, parenterally-fed, extremely-low-birth-weight infants, especially those having severely compromised cardiovascular or renal function, should be considered at greater risk of DEHP toxicity from repeated exposure to the plasticizer over prolonged periods of time.[19]

Possible solutions to this dilemma are to use PVC devices that do not contain DEHP (when commercially available), use devices that are made from other materials such as ethylene vinyl acetate, silicone, polyethylene or polyurethane, minimize procedure time to limit DEHP exposure, decrease the storage temperature when DEHP-containing products must be used, and use heparin-coated ECMO circuits.[6,24] Finally, developing an alternative to the currently used blood product storage bag to one that is non-DEHP containing is an identified priority.[46]

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REFERENCES

1. Report on Carcinogens, 10th ed. U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program, December 2002.
2. Wilkinson CF, Lamb JC. 4th. The potential health effects of phthalate esters in children's toys: review and risk assessment. Regulat Toxicol Pharmacol 1999;30:140-55.
3. Kavlock R, Boekelheide K, Chapin R, Cunningham M, Faustman E, Foster P, et al. NTP Center for the Evaluation of Risks to Human Reproduction: phthalates expert panel report on the reproductive and developmental toxicity of di(2-ethylhexyl) phthalate. Reprod Toxicol 2002;16:529-653.

4. Kaul AF, Souney PF, Osathanondh R. A review of possible toxicity of di-2-ethylhexylphthalate (DEHP) in plastic intravenous containers: effects on reproduction. Drug Intell Clin Pharm 1982;16:689-92.
5. Schultz CO. Assessing human health risks from exposure to di(2-ethylhexyl)-phthalate (DEHP) and related phthalates: scientific issues. Drug Metab Rev 1989;21:111-20.
6. Tickner JA, Schettler T, Guidotti T, McCally M, Rossi M. Health risks posed by use of Di-2-ethylhexyl phthalate DEHP) in PVC medical devices: a critical review. Am J Ind Med 2001;39:100-11.
7. Shea KM. Pediatric exposure and potential toxicity of phthalate plasticizers. Pediatrics 2003;11:1467-74.
8. Hillman LS, Goodwin SL, Sherman WR. Identification and measurement of plasticizer in neonatal tissues after umbilical catheters and blood products. N Engl J Med 1975;292:381-6.
9. Wallin FR, Klamer B, Nicora RW, Thompson CR. Di(2-ethylhexyl) phthalate (DEHP) metabolism in animals and post-transfusion tissue levels in man. Bull Parenter Drug Assoc 1974;28:278-87.
10. US Food and Drug Administration, Center for Devices and Radiological Health. Safety assessment of di(2-ethylhexyl) phthalate (DEHP) released from PVC medical devices. Rockville, MD: Center for Devices and Radiological Health; 2001. Available at http://www.noharm.org/details.cfm?ID=740&type=document. Accessed July 23, 2003.
11. Medical Devices Bureau, Therapeutic Products Directorate, Health Products & Foods Branch. Health Canada. DEHP in Medical Devices: An Exposure and Toxicology Assessment. Draft Report. Ottawa, Canada: Health Canada; 2001.
12. Hoyer PB. Reproductive toxicology: current and future directions. Biochem Pharmacol 2001;62:1557-64.
13. Sharpe RM. Hormones and testis development and the possible adverse effects of environmental chemicals. Toxicol Lett 2001;120:221-32.
14. Moore RM, Rudy TA, Lin T, Ko K, Peterson RE. Abnormalities of sexual development in male rats with in utero and lactational exposure to the antiandrogenic plasticizer di(2-ethylhexyl) phthalate. Environ Health Perspect 2001;109:229-37.
15. Baskin LS, Himes K, Colborn T. Hypospadias and endocrine disruption: Is there a connection? Environ Health Perspect 2001;109:1175-83.
16. Gangolli SD. Testicular effects of phthalate esters. Environ Health Perspect 1982;45:77-84.
17. Crisp TM, Clegg ED, Cooper RL,Wood WP, Anderson DG, Baetcke KP, et al. Environmental endocrine disruption: an effects assessment and analysis. Environ Health Perspect 1998;106 (supp 1):11-56.
18. Food and Drug Administration (FDA): Medical Devices Made with Polyvinyl chloride (PVC) using the Plasticizer di-(2-Ethylhexyl phthalate (DEHP): Draft Guidance for Industry and FDA. Center for Devices and Radiological Health, September 6, 2002. Available at http://www.fda.gov.cdrh/ode/guidance/1407.pdf. Accessed March 31, 2004.
19. Latini G. Potential hazards of exposure to di-(2-ethylhexyl)-phthalate in babies. Biol Neonate 2000;78:269-76.
20. Latini G, Avery GB. Materials degradation in endotracheal tubes: a potential contributor to bronchopulmonary dysplasia [letter]. Acta Paediatr 1999;88:1174-5.
21. Roth B, Herkenrath P, Lehman HJ, Ohles HD, Homig HJ, Benz-Bohm G, et al. Di-(2-ethylhexyl)-phthalate as plasticizer in PVC respiratory tubing systems: indications of hazardous effects on pulmonary function in mechanically ventilated, preterm infants. Eur J Pediatr 1988;147:41-6.
22. Hill SS, Shaw BR, Wu AHB. Plasticizers, antioxidants, and other contaminants found in air delivered by PVC tubing used in respiratory therapy. Biomed Chromatogr 2003;17:250-62.
23. Available at http://www.oehha.org/prop65/CRNR_notices/list_changes/6Ddehpnot.Html Accessed March 30, 2004.
24. Available at http://www.marketplaceatnovation.com/Pediatrics/Bulletins/2003/Qtr1/PedBullQ103.pdf (requires membership log-on) Accessed April 24, 2003.

25. Available at http://www.noharm.org/pvcDehp/issue. PVC/DEHP Audit Tool (PDF) Accessed April 25, 2003.
26. Available a: http://nohar.org/details.cfm?type=document&ID=717. Attaining 100% DEHP Elimination in IV Bags Miller Children's Hospital. (PDF) Accessed July 23, 2003.
27. Loff S, Kabs F, Witt K, Sartoris J, Mandl B, Niessen KH, et al. Polyvinyl infusion lines expose infants to large amounts of toxic plasticizers. J Pediatr Surg 2000;35:1775-81.
28. Loff S, Kabs F, Subotic U, Schaible T, Reinecke F, Langbein M. Kinetics of diethylhexyl-phthalate extraction from polyvinylchloride-infusion lines. JPEN J Parenter Enteral Nutr 2002; 26:305-9.
29. Kambia K, Dine T, Gressier B, Germe AF, Luyckx M, Brunet C, et al. High-performance liquid chromatographic method for the determination of di(2-ethylhexyl) phthalate in total parenteral nutrition and in plasma. J Chromatogr B Biomed Sci Appl 2001;755:297-303.
30. Mazur HI, Stennett DJ, Egging PK. Extraction of diethylhexylphthalate from total nutrient solution containing polyvinyl chloride bags. JPEN J Parenter Enteral Nutr 1989;13:59-62.
31. Jacobson MS, Sherwin VK, Grand RJ. Effects of a plasticizer leached from polyvinyl chloride on the subhuman primate: a consequence of chronic transfusion therapy. J Lab Clin Med 1977;89:1066-79.
32. Lovekamp-Swan T, Davis BJ. Mechanisms of phthalate ester toxicity in the female reproductive system. Environ Health Perspect 2003;111:139-45.
33. Dostal LA, Weaver RP, Schwetz BA. Transfer of di(2-ethylhexyl) phthalate through rat milk and effects on milk composition and the mammary gland. Toxicol Appl Pharmacol 1987;91:315-25.
34. Latini G, DeFelice C, Presta G, Del Vecchio A, Paris, Ruggieri F, et al. In Utero exposure to Di-(2-ethylhexyl) phthalate and duration of human pregnancy. Environ Health Perspect 2003;111: 1783-5.
35. Colon I, Caro D, Bourdony CJ, Rosario O. Identification of phthalate esters in the serum of young Puerto Rican girls with premature breast development. Environ Health Perspect 2000;108:895-900.
36. Sjoberg P, Bondesson U, Sedin G, Gustafsson J. Dispositions of di-and mono-(2-ethylhexyl) phthalate in newborn infants subjected to exchange transfusions. Eur J Clin Invest 1985;15:430-6.
37. Sjoberg POJ, Bondesson UG, Sedin EG, Gustafsson JP. Exposure of newborn infants to plasticizers. Plasma levels of di-(2-ethylhexyl) phthalate and mono-(2-ethylhexyl) phthalate during exchange transfusion. Transfusion 1985;25:424-8.
38. Calafat AM, Needham LL, Silva MJ, Lambert G. Exposure to Di-(2-Ethylhexyl) Phthalate Among Premature Neonates in a Neonatal Intensive Care Unit. Pediatrics 2004;113:e429-e434.
39. Guess WL. Safety evaluation of medical plastics. Clin Toxicol 1978;12:77-95.
40. Willhite CC. Weight-of-evidence versus strength-of-evidence in toxicologic hazard identification: di(2-ethylhexyl) phthalate (DEHP) Toxicology 2001;160:219-26.
41. Doull J, Cattley R, Lake BG, Swenberg J, Wilkenson C, Williams G, et al. A cancer risk assessment of Di(2-ethylhexyl) phthalate: application of the new U.S. EPA risk assessment guidelines. Regul Toxicol Pharmacol 1999;29:327-57.
42. Hussain N, Chaghtai A, Herndon CDA, Herson VC, Rosenkrantz TS, McKenna PH. Hypospadias and early gestation growth restriction in infants. Pediatrics 2002;109:473-8.
43. Axelrod D, Davis DL, Jones LA. It's time to rethink dose: the case for combining cancer and birth and developmental effects. Environ Health Perspect 2001;109(A):246-9.
44. Cairns J Jr. Interrelationships between the precautionary principle, prediction strategies and sustainable use of the planet. Environ Health Perspect 2003;111:877-80.
45. Kriebel D, Tickner J, Epstein P, Lemons J, Levins R, Loechler EL, et al. The precautionary principle in environmental science. Environ Health Perspect 2001;109:871-6.
46. Rubin RL, Ness PM. What price progress? An update on vinyl plastic blood bags. Transfusion 1989;29:358-61.