February 7, 2003

Dibutyl Phthalate, Diethyl Phthalate, and Dimethyl Phthalate Re-review Summary

On November 19, 2002 the CIR Expert Panel announced its decision to not reopen the safety assessment of the Dibutyl Phthalate group of ingredients. The Panel asked that the summary of the newly available data and a discussion of the issues be prepared for their review. That was done and the summary was approved on February 7, 2003. Interested persons are invited to comment on or before April 11, 2003.

Dibutyl Phthalate, Diethyl Phthalate, and Dimethyl Phthalate

A safety assessment of Dibutyl Phthalate (DBP), Diethyl Phthalate (DEP), and Dimethyl Phthalate (DMP) was published in 1985 with the conclusion that these ingredients "are safe for topical application in the present practices of use and concentrations in cosmetics" (Elder, 1985). Since then many additional studies have appeared in the scientific literature. These studies, along with the updated information in Tables 1 - 3 regarding uses and use concentrations, were considered by the CIR Expert Panel. Based on its consideration of the data discussed below, the Panel decided not to reopen this safety assessment.

DBP, DEP, and DMP are phthalate diesters that are used in cosmetics as plasticizers, solvents and fragrance ingredients in a wide variety of cosmetic product types. DEP is also used as a denaturant. DBP is found primarily in nail care products (at concentrations up to 15 %) and in some hair care formulations (up to 0.1 %). DEP is found in certain bath preparations, fragrance products, deodorants, lotions, and other skin care products. The highest reported concentration of use of DEP is 11 % in perfumes. DMP is an ingredient in some hair care products, including aerosol fixatives. The reported maximum concentration of use of DMP in cosmetics is 2 % in aerosol hair sprays. Tables 1 - 3 provide the frequency and concentration of use as a function of product type.

Recent studies document that DBP, DEP, and DMP all absorb readily through the skin and through the GI tract. Once absorbed, most short-chain phthalate diesters are hydrolyzed to the corresponding monoester and alcohol. The phthalates and their metabolites distribute to most tissues, and cross the placenta, but they do not accumulate in any specific tissue type. Phthalates are quickly eliminated in the urine, usually as the corresponding monoester or its glucuronide conjugate. However, humans and primates metabolize longer-chain diester phthalates (e.g., DEHP) into the glucuronide-conjugated monoester forms to a much larger extent than do rats. Also, rats excrete three to four times more free unconjugated MBP than do hamsters given similar doses of DBP or MBP, possibly due to greater testicular β-glucuronidase activity in rats than in hamsters. Phthalates undergo some enterohepatic cycling, and some phthalate is eliminated in the feces.

New data on acute and short-term toxicity were consistent with previously available data.

In a National Toxicology Program (NTP) study, DBP, DEP, and DMP were not found to be dermal irritants or sensitizers, confirming previous data using human and animal subjects.

While previous data had identified that orally administered (in feed or by gavage) DBP and its metabolite MBP have reproductive and developmental effects in rodents, with impaired male development being the most sensitive effect, newly available data provided additional demonstration of such effects.

When pregnant rats and mice were exposed to 1.0 % DBP in powdered feed throughout gestation, the pregnancy outcome showed reductions in fertility, number of pups per litter, number of live pups, and body weights of pups. Adult male rats exposed to 1.0 % DBP showed signs of liver and kidney toxicity and reduced weights of the prostate, testes, and seminal vesicles. Pregnant rats exposed to 2 % DBP in feed throughout pregnancy had a higher incidence of preimplantation loss and resorptions, and no male pups were born alive. Exposure to 1 or 2 % DBP in feed only during the latter half of gestation did not show the preimplantation loss and resorption rate seen in rats exposed throughout pregnancy. However, the increased survivability of these fetuses allowed the morphological defects of developing fetuses to be observed. These defects included reduced body weights in both sexes at 2 % DBP, reduced anogenital distance and undescended testes in male fetuses at 1 and 2 % DBP, and increased incidence of cleft palate and fused sternebrae. Adverse fetal effects were not seen in this study at a 0.5 % DBP feed group, or 331 mg/kg/day based on average food consumption.

Oral intubation (gavage) of DBP in rats during gestation produced similar effects to those seen in the feeding studies described above. Pregnant rats given oral doses of approximately 0.63 to 0.75 g/kg/day and higher on certain gestation days produced litters with higher incidences of fetal toxicity and malformations. Exposure to DBP on gestation days 7 through 9 or on days 13 through 15 results in increased incidence of skeletal malformations such as cleft palate, fused sternebrae, and vertebral anomalies, as well as dilatation of the renal pelvis and undescended testes. However, exposure to DBP on gestation days 10 through 12 did

not produce these effects, suggesting that DBP teratogenicity may be age-dependent. Prenatal exposure to MBP appears to produce fetotoxicity and teratogenicity similar to DBP, following the same patterns of age-dependent sensitivity and dose efficacy. This supports the proposal that it is the monoester metabolite that produces the developmental toxicity of DBP and other phthalates.

DEP fed to mice at concentrations up to 2.5 % (calculated to be 3.64 g/kg/day) in a continuous breeding protocol produced no effects of DEP on fertility or pregnancy outcome in the F_0 generation. F_1 male mice of the 2.5 % DEP group had enlarged prostates and reduced sperm counts, but sperm motility and morphology were not affected. The F_2 generation showed no treatment-related differences between DEP and control groups. Pregnant rats fed up to 5.0 % DEP mixed in feed on gestation days 6 through 15 produced no treatment-related alterations in fetal viability or development.

Repeated dermal application of 2 ml/kg up to 50 % DEP to pregnant rabbits on gestation days 6 through 18 did not produce maternal or fetal toxicity or affect fetal development.

DMP was not fetotoxic or teratogenic when administered dermally (in rats) or orally (in rats and mice) during gestation.

Exposure to some phthalates has been shown to cause impairments of normal male development in rodents. The documented male-specific effects of phthalates include malformations of the epididymis and vas deferens, undescended testes, hypospadias, retention of thoracic nipples, and reduced anogenital distance. DEP and DMP did not cause the dramatic effects on male development seen with longer-chain dialkyl phthalates. Many studies have reviewed the mechanisms of the male-targeted toxicity of phthalates. DBP, DEP, and DMP have weak or no binding affinity for estrogen receptor and do not affect estrogen-regulated developmental endpoints. An anti-androgenic mechanism has been proposed, but many studies show that these phthalates do not bind with androgen receptors, either. However, phthalate esters inhibit the synthesis of testosterone, which is an important hormone in normal development in males. DBP has also been shown to inhibit the action of Müllerian Inhibiting Substance produced by Sertoli cells.

DBP, DEP, and DMP previously had been screened for mutagenicity in the Ames bacterial reverse mutation assay with no mutagenic potential found. Additional data were available reporting that DBP caused an increase in the number of TA100 revertants in the absence but not in the presence of S9 rat liver fraction. DEP caused increases in the numbers of TA100 and TA1535 revertants, but this effect was also eliminated by the presence of S9. DMP caused an increase in the number of TA1535 revertants, but S9 prevented the effect. Overall, DBP, DEP, and DMP continue to have little genotoxic potential. One study on males of subfertile couples examined the relationship between environmental exposures to phthalates and DNA damage in human sperm using the neutral comet assay which is said to measure at least two aspects of DNA integrity. Neither the monobutyl form of DBP nor DMP had a significant association with comet assay parameters, and a significant association with the monobutyl form of DEP was seen only with one measure of DNA integrity.

Phthalates are a matter of concern for those responsible for public health and have been (and continue to be) reviewed by many government and international organizations. Phthalates are ubiquitous in the modern environment. The monoester metabolites of phthalates have been detected in the urine of an adult reference population and in the urine of young children in a small pilot study. Environmental exposure to phthalates and other endocrine disruptors have been proposed to be linked to an increased incidence of hypospadias in humans. The developmental effects of phthalates seen in rodents raise questions about the potential for human health risks. However, these effects seen in rodents are at much higher exposure levels than humans are likely to encounter, and they are subject to the species differences in the metabolism of phthalate diesters. The estimated median exposure levels of DEP and DBP are 57 µg/kg/day and 7 µg/kg/day, respectively, while the U.S. EPA reference doses (RfD) for DEP and DBP are 800 µg/kg/day and 100 µg/kg/day, respectively. Thus, the human exposure is well below the safety limits set by the U.S. EPA. Even the median exposure levels of the highest-exposed group (women aged 20 to 40 years) are well below the RfD's. Exposure levels were not available for DMP.

Scientific committees with the governments of the United States and the European Union have evaluated the human risks of DBP and DEP and expressed minimal to no concern over consumer exposure to these

compounds (National Toxicology Program's Center for the Evaluation of Risks to Human Reproduction, 2000; Netherlands Organization for Applied Scientific Research and National Institute of Public health and the Environment, 200; Scientific Committee on Cosmetic Products and Non-Food Products, 2002).

As in the original safety assessment of these phthalate diesters in 1984, the primary safety issue regarding phthalate esters in this re-review is anti-androgenic activity and the potential effects on male development. The CIR Expert Panel noted that the free monoester metabolite appears to be the active agent in phthalate diester toxicity. Of the three compounds reviewed in this safety assessment, Dibutyl Phthalate raised the most concern.

The Panel reviewed the numerous studies that describe the developmental toxicity of DBP in rodents. The Panel noted that the no observed adverse effect level (NOAEL) of DBP in a gavage study was 50 mg/kg/day (Mylchreest et al., 2000). However, a feeding study reported a NOAEL of 331 mg/kg/day (Ema et al., 1998). Overall, the Panel felt that feeding studies better represent of the type of exposure that humans would receive from cosmetics than do gavage studies, but agreed that a worst-case NOAEL of 50 mg/kg/day should be considered.

The Panel considered a Margin of Safety (MOS) approach to assess the risk of DBP exposure to human users of cosmetics based on calculated exposures and the animal developmental toxicity data. Exposure calculations were based on ingredient concentration of use in cosmetic products (CTFA, 2001a, b, c; Houlihan et al., 2002), extent of cosmetic use survey data (Environ Corporation, 1985; CTFA, 2002b), and dermal (Mint et al., 1994) and subungual penetration data (Jackson Research Association, 2002). A conservative approach to penetration was used; i.e., an estimate of approximately 5 % absorption of DEP in human skin was considered to be a conservative estimate of DBP absorption, because data suggest that DEP is more readily absorbed in rat skin than DBP (Scott et al., 1987). The Panel used an estimated consumer body weight of 60 kg.

The expected exposure was calculated as follows:

Nail basecoat or polish

- 280 mg/application to 10 fingernails (Environ Corporation, 1985)
- 15 % maximum DBP in nail basecoats and polish (CTFA, 2001a, b, c; Houlihan et al., 2002)
- 8.5 % penetration through nail in 14 days (Jackson Research Association, 2002)

280 mg/day x 15% x 8.5% / 14 days = 0.255 mg/day / 60 kg = 4.25 µg/kg/day

4.5 µg/kg/day x 2 (for fingers and toes) = 8.5 µg/kg/day.

Hair Spray

- 5 g/day hair spray use(CTFA, 2002)
- 160 µg/g DBP in hair spray (Houlihan et al., 2002)
- 20% skin contact, from CTFA maximum worst case estimates
- 5% skin absorption (Mint et al., 1994)

5 g/day x 160 µg/g x 20% x 5% = 8 µg/day / 60 kg = 0.14 µg/kg/day.

Deodorant

- 0.52 g/day deodorant use (Environ Corporation, 1984)
- 200 µg/g DBP in deodorant (Houlihan et al., 2002)
- 5 % skin absorption (Mint et al., 1994)

0.52 g/day x 200 µg/g x 5% = 5.2 µg/day / 60 kg = 0.09 µg/kg/day.

Perfume

- 0.53 g/day perfume use (CTFA, 2002)
- 890 µg/g DBP in perfume (Houlihan et al., 2002)
- 5% skin absorption (Mint et al., 1994)

0.53 g/day x 890 µg/g x 5% = 24 µg/day / 60 kg = 0.4 µg/kg/day.

Total Exposure

8.5 µg/kg/day + 0.14 µg/kg/day + 0.09 µg/kg/day + 0.4 µg/kg/day = 9.13 µg/kg/day

The calculated estimated exposure level of DBP from the concurrent use of multiple cosmetic products came to 9.13 µg/kg/day. This value is within the reported range of total human exposure to DBP from all sources in women, 32 µg/kg/day (upper 95th percentile for women of reproductive age) to 6.5 µg/kg/day (upper 95th percentile for rest of group). Therefore, the Panel accepted 9.13 µg/kg/day as a not unreasonable approximation of DBP exposure from cosmetic products.

The Panel calculated the MOS of DBP by dividing the NOAEL of 331 mg/kg/day (from a feeding study) by the expected exposure 9.13 µg/kg/day, yielding an MOS of 36,254. If the more conservative NOAEL of 50 mg/kg/day (from a gavage study) is used, the MOS is 5,476. The Panel also noted that both NOAEL figures were obtained from rat studies, and detoxication metabolism of DBP is faster in humans than in rats.

The Panel acknowledged the use of DBP, DEP, and DMP in hair sprays. The effects of inhaled aerosols depend on the specific chemical species, the concentration, the duration of exposure, and site of deposition (Jensen and O'Brien, 1993) within the respiratory system. Particle size is the most important factor affecting the location of deposition. The mean aerodynamic diameter of pump hair spray particles is approximately 80 µm, and the diameter of anhydrous hair spray particles is 60-80 µm. Typically less than 1% are below 10 µm which is the upper limit for respirable particles (Bowen, 1999). Based on the particle size, DBP, DEP, and DMP would not be respirable in formulation. Therefore, exposure of the lung by inhalation was not considered likely.

Based on the available information included in this report, the CIR Expert Panel concluded that Dibutyl Phthalate, Dimethyl Phthalate, and Diethyl Phthalate are safe for use in cosmetic products in the present practices of use and concentrations, and therefore, the safety assessment of these compounds was not reopened.

Table 1. Current and historical concentration of use data for Dibutyl Phthalate

	1981 Data		2001 Data	
Product Category	No. of formulations containing ingredient (FDA, 1981)	Concentration range in cosmetic products (FDA, 1981)	No. of formulations containing ingredient (FDA, 2001)	Current Concentration of Use (CTFA, 2001a; 2001b; 2001c)
Other manicuring preparations	14	≤25 %	25	5 - 7 % 6 %[1]
Nail polish and enamel removers	3	0.1 - 25 %	-	2 %
Nail creams and lotions	-	-	2	5 %
Nail extenders	-	-	-	1 % 1 %[1]
Nail polish and enamel	522	≤25 %	88	0.5 - 15 % 15 %[1]
Basecoats and undercoats (manicuring preparations)	36	>1 - 10 %	32	1 - 6 % 15 %[1]
Other makeup preparations	1	>0.1 - 1 %	-	0.5 %
Other hair preparations (noncoloring)	3	>0.1 - 1 %	-	-
Other hair coloring preparations	3	>0.1 - 1 %	-	0.1 %
Aftershave lotions	3	>0.1 - 1 %	-	-
Hair bleaches	-	-	-	0.1 %
Shampoos (noncoloring)	-	-	-	0.007 %
Fragrance	-	-	-	38 - 890 ppm[2]
Deodorant	-	-	-	140 - 200 ppm[2]
Hair Spray	-	-	-	55 - 160 ppm[2]
Other personal cleanliness products	5	>1 - 5 %	3	-
Total frequency of use for DBP	**590**		**150**	

[1] Maximum Concentrations reported by Nail Manufacturers Council (NMC, 2001).
[2] Concentrations found in off-the-shelf products (Houlihan et al. 2002).

Table 2. Current and historical concentration of use data for Diethyl Phthalate

	1981 Data		2001 Data	
Product Category	No. of formulations containing ingredient (FDA, 1981)	Concentration range in cosmetic products (FDA, 1981)	No. of formulations containing ingredient (FDA, 2001)	Current Concentration of Use (CTFA, 2001a; 2001b; 2001c)
Bath oils, tablets, and salts	3	≤5 %	1	-
Other bath preparations	2	≤0.1 %	2	-
Baby shampoos	-	-	-	0.03 %
Baby lotions, oils, powders, and creams	-	-	-	0.00003 %
Other baby products	-	-	-	0.05 %
Bubble baths	-	-	-	0.06 %
Other bath preparations	-	-	-	0.008 - 0.09 %
Shampoos (noncoloring)	-	-	-	0.0008 - 0.2 %
Bath soaps and detergents	1	>0.1 - 1 %	-	2 %
Hair conditioners	-	-	-	0.1 - 0.2 %
Hair sprays (aerosol fixatives)	5	>0.1 - 5 %	-	0.4 % 17 - 1500 ppm[1]
Hair gels	-	-	-	14 - 220 ppm[1]
Hair mousse	-	-	-	38 - 75 ppm[1]
Wave sets	1	>0.1 - 1 %	-	-
Face powders	-	-	-	0.4 %
Eye shadow	1	≤0.1 %	-	-
Eyebrow pencil	-	-	-	0.007 %
Mascara	-	-	-	0.007 - 0.07 %
Other eye makeup preparations	-	-	-	0.07 %
Foundations	-	-	-	0.3 %
Lipstick	-	-	-	0.00005 %
Other makeup preparations	-	-	-	0.0003 %
Nail polish and enamel remover	1	>1 - 5 %	-	-
Nail polish and enamel	-	-	-	0.1 %
Other manicuring preparations	-	-	-	0.2 %
Colognes and toilet waters	19	≤5 %	24	0.2 - 2 %
Perfumes	23	≤50 %	7	1 -11 %
Powders	1	>0.1 - 1 %	5	-
Sachets	3	>0.01 - 5 %	2	-
Other fragrance preparations	2	>0.1 - 50 %	11	0.01 - 1 % 67 - 28,000 ppm[1]
Tonic, dressings, and other hair grooming aids	-	-	1	-
Deodorants	-	-	4	0.3 - 1 % 20 - 3300 ppm[1]
Feminine hygiene deodorants	-	-	-	0.4 %
Other personal cleanliness products	-	-	-	1 %
Aftershave lotion	3	>0.1 - 1 %	4	0.5 - 2 %

Table 2 *continued.* Current and historical concentration of use data for Diethyl Phthalate

Product Category	1981 Data: No. of formulations containing ingredient (FDA, 1981)	1981 Data: Concentration range in cosmetic products (FDA, 1981)	2001 Data: No. of formulations containing ingredient (FDA, 2001)	2001 Data: Current Concentration of Use (CTFA, 2001a; 2001b; 2001c)
Shaving cream (aerosol, brushless, and lather)	-	-	-	0.001 %
Other shaving preparation products	-	-	-	1 %
Skin cleansing (cold creams, cleansing, lotions, liquids and pads)	-	-	-	0.0002 %
Face and neck creams, lotions, powders, and sprays (excluding shaving preparations)	1	≤0.1 %	-	0.3 %
Body and hand creams, lotions, powders, and sprays	-	-	2	0.008 - 0.5 % 26 - 190 ppm[1]
Foot powders and sprays	-	-	-	1 %
Night creams, lotions, powders, and sprays (excluding shaving preparations)	-	-	-	0.0004 %
Paste masks (mud packs)	-	-	1	0.1 %
Skin fresheners	-	-	4	0.1 - 0.9 %
Other skin care preparations	1	>0.1 - 1 %	5	0.00003 - 0.9 %
Total frequency of use for DEP	67		73	

[1] Concentrations found in off-the-shelf products (Houlihan et al. 2002).

Table 3. Current and historical concentration of use data for Dimethyl Phthalate

Product Category	1981 Data: No. of formulations containing ingredient (FDA, 1981)	1981 Data: Concentration range in cosmetic products (FDA, 1981)	2001 Data: No. of formulations containing ingredient (FDA, 2001)	2001 Data: Current Concentration of Use (CTFA, 2001a; 2001b; 2001c)
Hair sprays (aerosol fixatives)	-	-	8	0.00002 - 2 %
Other hair preparations	4	>0.1 - 1 %	3	-
Hair color sprays (aerosol)	-	-	1	-
Shampoos (noncoloring)	-	-	-	0.00002 %
Hair conditioners	2	>0.1 - 1 %	-	-
Tonics, dressings, and other hair grooming aids	2	>0.1 - 5 %	-	-
Hair rinses	1	>0.1 - 1 %	-	-
Wave sets	2	>0.1 - 1 %	-	-
Blushers (all types)	-	-	-	0.00008 %
Face powders	-	-	-	0.00008 %
Foundations	-	-	-	0.005 %
Bath soaps and detergents	-	-	-	0.004 %
Deodorants (underarm)	-	-	-	0.2% 33 ppm[1]
Aftershave lotions	-	-	-	0.2 %
Total frequency of use for DMP	11		12	

[1] Concentration found in off-the-shelf products (Houlihan et al. 2002).

REFERENCES

Agarwal, D.K., W. H. Lawrence, L. J. Nunez, and J. Autian. 1985. Mutagenicity evaluation of phthalic acid esters and metabolites in Salmonella Typhimurium cultures. *Journal of Toxicology and Environmental Health* 16: 61-69.

Agency for Toxic Substances and Disease Registry. 1995. Toxicological profile for diethyl phthalate. NTIS Report No. PB95264214.

Albro, P. W. 1986. Absorption, metabolism, and excretion of di(2-ethylhexyl)phthalate by rats and mice. *Environ. Health Perspect.* 65: 293-298.

Anderson, W. A., L. Castle, M. J. Scotter, R. C. Massey and C. Springall. 2001. A biomarker approach to measure human dietary exposure to certain phthalate diesters. Food Addit. Comtam. 18(12): 1068-74.

Api, A. M. 1997. *In vitro* assessment of phototoxicity. *In Vitro Toxicology.* 10(3): 339-350.

Api, A. M. 2001. Toxicological profile of diethyl phthalate: a vehicle for fragrance and cosmetic ingredients. Food Chem. News. 39: 97-108.

Bagley, D. M., J. R. Garner, G. Holland, R. W. Lewis, J. -F. Regnier, D. A. Stringer, and A. P. Walker. 1996. Skin Irritation: reference chemicals data bank. *Toxicol. In Vitro.* 10: 1-6.

Barber, E. D., M. Cifone, J. Rundell, R. Pryzgoda, B. D. Astill, E. Moran, A. Mulholland, E. Robinson, and B. Schneider. 2000. Results of the L5178Y mouse lymphoma assay and the Balb/3T3 cell *in vitro* transformation assay for eight phthalate esters. *J. Appl. Toxicol.* 20: 69-80.

Baskin, L. S., K. Himes, and T. Colborn. 2001. Hypospadias and endocrine disruption: Is there a connection? *Environ. Health Perspect.* 109(11). 1175-1183.

BASF. no date. Di-n-butyl phthalate - subacute inhalation study in Wistar rats 20 exposition as a liquid aerosol. Unpublished data submitted by Phthalate Esters Panel, American Chemistry Council (57 pages). Note: this is a draft report that had apparently not been audited for quality assurance.

BASF. 1992. Study on the oral toxicity of dibutyl phthalate in Wistar rats. Administration via the diet over 3 months. Unpublished data submitted by Phthalate Esters Panel, American Chemistry Council (369 pages).

BASF. 1999. Di-n-butyl phthalate - subacute inhalation study in Wistar rats. 20 exposures as a liquid aerosol. Unpublished data submitted by Phthalate Esters Panel, American Chemistry Council (189 pages).

Blair, R. M., H. Fang, W. S. Branham, B. S. Hass, S. L. Dial, C. L. Moland, W. Tong, L. Shi, R. Perkins, and D. M. Sheehan. 2000. The estrogen receptor relative binding affinities of 188 natural and xenochemicals: structural diversity of ligands. *Toxicol. Sci.* 45: 138-153.

Blount, B. C., M. J. Silva, S. P. Caudill et al. 2000. Levels of seven urinary phthalate metabolites in a human reference population. *Environmental Health Perspectives* 108(10): 979-982.

Bower D (1999) Unpublished information on hair spray particle size provided at the September 9, 1999 CIR Expert Panel meeting.

Brock, J. W., S. P. Caudill, M. J. Silva, L. L. Needham, and E. D. Hilborn. 2002. Phthalate monoesters levels in the urine of young children. Bull. Environ. Contam. Toxicol. 68: 309-314.

Butala, J., M. Moore, M. Cifone, J. Bankston, and B. Astill. 1996. Oncogenicity study of di(isononyl) phthalate in rats. *Toxicologist.* 30: 202.

Butala, J., M. Moore, M. Cifone, J. Bankston, and B. Astill. 1997. Oncogenicity study of di(isononyl) phthalate in mice. *Toxicologist.* 36: 173.

Castle, L., A. Mercer, J. R. Startin, and J. Gilbert. 1988. Migration from plasticized films into foods 3. Migration of phthalate, sebacate, citrate and phosphate esters from films used for retail food packaging. *Food Additives and Contaminants* 5(1): 9-20.

Chu-Tse, W., P. Xue-Tao,C. Jun-Rong, and X. Hui-Hua. 1993. A new pharmacological activity of dibutyl phthalate (dbp) on selective elimination of tumor cells from bone marrow. *Leukemia Research* 17(7): 557-560.

Colón, A., D. Caro, C. J. Bourdony, and O. Rosario. 2000. Identification of phthalate esters in the serum of young Puerto Rican girls with premature breast development. *Environ. Health Perspectives.* 108(9): 895-900.

Consumer Product testing. 1978a. Oral LD50 (rat) study no. 78-032. Unpublished data submitted by CTFA (13 pages).

Consumer Product testing. 1978b. Dermal LD50 (rat) study no. 78-033. Unpublished data submitted by CTFA (13 pages).

Consumer Product testing. 1978c. Guinea pig sensitization study no. 78-034. Unpublished data submitted by CTFA (13 pages).

Cosmetic, Toiletry, and Fragrance Administration (CTFA). 2001a. Unpublished data regarding current concentrations of cosmetic uses of Dibutyl Phthalate. January 4, 2001. (2 pages).

CTFA. 2001b. Unpublished data regarding current concentrations of cosmetic uses of Dibutyl Phthalate. April 20, 2001. (2 pages).

CTFA. 2001c. Unpublished data regarding current concentrations cosmetic uses of Dimethyl and Diethyl Phthalate. October 18, 2001. (2 pages).

CTFA. 2001d. Unpublished data available on the CTFA International Cosmetic Legal & Regulatory Database Global Ingredient Search.

CTFA, 2002a. Unpublished data regarding physical properties of dibutyl phthalate. Submitted August 30, 2002. (3 pages.)

CTFA, 2002b. Unpublished data regarding average hairspray and perfume use. June 26, 2002. (3 pages)

Cummings, A.M. and L. E. Gray. 1987. Dibutyl Phthalate: maternal effects versus fetotoxicity. *Toxicology Letters*. 39: 43-50.

David. R.,M. Moore, M. Cifone, D. Finney, and D. Guest. 1999. Chronic peroxisome proliferation and hepatomegaly associated with the hepatocellular tumorigenesis of di(2-ethylhexyl)phthalate and the effects of recovery. *Toxicol. Sci.* 50: 195-205.

David, R.M. 2000. Exposure to phthalate esters. *Environ. Health Perspectives.* 108(10): A440.

Dirven, H., P. H. H. Vandenbroek, A. M. M. Arends, H. H. Nordkamp, A. Delepper, P. T. Henderson, and F. J. Jongeneelen. 1993. Metabolites of the plasticizer di(2-ethylhexyl) phthalate in urine samples of workers in polyvinylchloride processing industries. *Int. Arch. Occup. Environ. Health*. 64: 549-554.

Duty, S.M., N.P. Singh, M.J. Silva, D.B. Barr, J.W. Brock, L. Ryan, R.F. Herrick, D.C. Christiani, and R. Hunter. 2002. The relationship between environmental exposures to phthalates and DNA damage in human sperm using the neutral comet assay. *Environ Health Perspect*. available at http://dx.doi.org/doi:10.1289/ehp.5756.

E. I. du Pont de Nemours and Company. 1946. Possibility of dermatitis from dimethyl phthalate when used as an insect repellant. Unpublished data collected Haskell Laboratory of Industrial Toxicology and submitted by Phthalate Esters Panel, American Chemical Council (2 pages).

E. I. du Pont de Nemours and Company. 1970. Skin primary irritation and sensitization test on guinea pigs. Unpublished data collected Haskell Laboratory for Toxicology and Industrial Medicine and submitted by Phthalate Esters Panel, American Chemical Council (2 pages).

E. I. du Pont de Nemours and Company. 1974. Dimethyl phthalate. Unpublished data collected Haskell Laboratory for Toxicology and Industrial Medicine and submitted by Phthalate Esters Panel, American Chemical Council (2 pages).

Elsisi, A. E., D. E. Carter, and I. G. Sipes. 1989. Dermal absorption of phthalate diester in rats. *Fundamental and Applied Toxicology*. 12:70-77.

Ema, M., H. Amano, T. Itami, and H. Kawasaki. 1993. Teratogenic evaluation of di-n-butyl phthalate in rats. *Toxicology Letters*. 69: 197-203.

Ema, M., H. Amano, and Y. Ogawa. 1994. Characterization of the developmental toxicity of di-n-butyl phthalate in rats. *Toxicology*. 86: 163-174.

Ema, M., A. Harazono, E. Miyawaki, and Y. Ogawa. 1997a. Developmental effects of di-n-butyl phthalate after a single administration in rats. *J Applied Toxicol.* 17(4): 223-229.

Ema, M., A. Harazono, E. Miyawaki, and Y. Ogawa. 1997b. Embryolethality following maternal exposure to dibutyl phthalate during early pregnancy in rats. *Bull Environ Contam Toxicol*. 58: 636-643.

Ema, M., R. Kurosaka, H. Amano, and Y. Ogawa. 1995a. Comparative developmental toxicity of n-butyl benzyl phthalate and di-n-butyl phthalate in rats. *Arch Environ Contam Toxicol.* 28: 223-228.

Ema, M., R. Kurosaka, H. Amano, and Y. Ogawa. 1995b. Developmental toxicity evaluation of mono-n-butyl phthalate in rats. *Toxicology Letters*. 78: 101-106.

Ema, M., R. Kurosaka, A. Harazono, H. Amano, and Y. Ogawa. 1996. Phase specificity of developmental toxicity after oral administration of mono-n-butyl phthalate in rats. *Arch. Environ. Contam. Toxicol.* 31: 170-176.

Ema, M. and E. Miyawaki. 2001a. Adverse effects on development of the reproductive system in male offspring given monobutyl phthalate, a metabolite of dibutyl phthalate, during late pregnancy. *Reproductive Toxicol.* 15: 189-194.

Ema, M. and E. Miyawaki. 2001b. Effects of monobutyl phthalate on reproductive function in pregnant and pseudopregnant rats. *Reproductive Toxicol.* 15: 261-267.

Ema, M., E. Miyawaki, and K. Kawashima. 1998. Further evaluation of developmental toxicity of di-n-butyl phthalate following administration during late pregnancy in rats. *Toxicology Letters.* 98: 87-93.

Ema, M., E. Miyawaki, and K. Kawashima. 2000a. Critical period for adverse effects on development of reproductive system in male offspring of rats given di-n-butyl phthalate during late pregnancy. *Toxicology Letters.* 111: 271-278.

Ema, M., E. Miyawaki, and K. Kawashima. 2000b. Effects of dibutyl phthalate on reproductive function in pregnant and pseudopregnant rats. *Reproductive Toxicology.* 14: 13-19.

Environ Corporation. 1984. Summary of the Results of Surveys of the Amount and Frequency of Use of Cosmetic Products by Women. Unpublished report submitted by CTFA. (7 pages)

Environment Canada. 1994. Canadian environmental protection act priority substances list assessment report: dibutyl phthalate. NTIS Report No. PB94169059.

Epstein, W. L. 1978. Human sensitization study of diethyl phthalate. Unpublished data submitted by CTFA (4 pages).

Essex Testing Clinic, Inc. 1989. Clinical safety evaluation of diethyl phthalate in repeated insult patch test, with cover letter dated 05/09/94 (sanitized). NTIS Report No. OTS0557309.

Essex Testing Clinic, Inc. 1990. Final report, clinical safety evaluation of test article diethyl phthalate control (neat); repeated insult patch test with cover letter dated 05/09/94 (sanitized). NTIS Report No. OTS0557311.

European Commission. 2002. The rules governing cosmetic products in the European Union. Volume 1. Cosmetics legislation - Cosmetic products. Accessed April 22, 2002 http://dg3.eudra.org/F3/home.html.

Field, E. A., C. J. Price, R. S. Sleet, J. D. George, M. C. Marr, C. B. Myers, B. A. Schwetz, and R. E. Morrissey. 1993. Developmental Toxicity evaluation of diethyl and dimethethyl phthalate in rats. *Teratology.* 48: 33-44.

Food and Drug Administration (FDA). 2001. Frequency of use of cosmetic ingredients. *FDA Database.* Washington: FDA.

Foster P. M., M. W. Cook, L. V. Thomas, D. G. Walters and S. D. Gangolli. 1983. Differences in urinary metabolic profile from di-n-butyl phthalate-treated rats and hamsters. A possible explanation for species differences in susceptibility to testicular atrophy. Drug Metab. Dispos. 11(1): 59-61.

Foster, P. M. D., R. C. Cattley, and E. Mylchreest. 2000. Effects of di-n-butyl phthalate (DBP) on male reproductive development in the rat: implications for human risk assessment. *Food and Chemical Toxicology* 38: S97-S99.

Fredricsson, B., L. Möller, Å. Pousette, and R Westerholm. 1993. Human sperm motility is affected by plasticizers and diesel particle extracts. *Pharmacology & Toxicology.* 72: 128-133.

Fukuoka, M., T. Kobayashi, Y. Zhou, and T Hayakawa. 1993. Mechanism of testicular atrophy introduced by di-n-butyl phthalate in rats. Part 4. Changes in the activity of succinate dehydrogenase and the levels of transferrin and ferritin in the Sertoli and germ cells. *Journal of Applied Toxicology.* 13(4): 241-246.

Fukuoka, M., S. Nhmi, Y. Zhou, T. Kobayashi, anf T. Hayakawa. 1996. Responsiveness of rat nonparenchtmal liver cells and spleen cells to the decomposition of erythrocytes exposed to di-n-butyl phthalate and its metabolite. *Biol Pharm Bull.* 19(9): 1154-1159.

Fukuoka, M., T. Tanimoto, Y. Zhou, N. Kawasaki, and A Tanaka. 1989. Mechanism of testicular atrophy by di-n-butyl phthalate in rats. Part 1. *Journal of Applied Toxicology.* 9: 277-283.

Fukuoka, M., Y. Zhou, A. Tanaka, I. Ikemoto, and T. Machida. 1990. Mechanism of testicular atrophy induced by di-n-butyl phthalate in rats. Part 2. The effects on some testicular enzymes. *Journal of Applied Toxicology.* 10(4): 285-293.

Gall, H., A. Köhler, and R. U. Peter. 1999. Anaphylactic shock reaction to dibutyl-phthalate-containing capsules. *Dermatology.* 199: 169-170.

Gray TJB, Rowland IR, Foster PMD, Gangolli SD. (1982) Species differences in the testicular toxicity of phthalate esters. *Toxicology Letters* 11: 141-147.

Gray, L. E., J. Ostby, J. Furr, M. Price, D. N. Veeramachaneni, and L. Parks. 2000. Perinatale exposure the the phthalates DEHP, BBP, and DINP, but not DEP, DMP, or DOTP, alters sexual differentiation of the male rat. *Toxicol. Sci.* 58: 350-65.

Gray, L. E., C. Wolf, C. Lambright et al. 1999. Administration of potentially antiandrogenic pesticides (procymidone, linuron, iprodione, chlozolinate, p,p'-DDE, and ketoconazole) and toxic substances (dibutyl- and diethylhexyl phthalate, PCB 169, and ethane dimethane sulphonate) during sexual differentiation produces diverse profiles of reproductive malformations in the male rat. *Toxicology and Industrial Health.* 15: 94-118.

Hall, M., A. Mathews, L. Webley, and R. Harling. 1999. Effects of di-isononyl phthalate (DINP) on peroxisomal markers in the marmoset-DINP is not a peroxisome proliferator. *J. Toxicol. Sci.* 24: 237-244.

Hansen, E. and O. Meyer. 1989. No embryotoxic or teratogenic effect of dimethyl phthalate in rats after epicutaneous application. *Pharmacol. & Toxicol.* 64: 237-238.

Harris, C. A., P. Henttu, M. G. Parker, and J. P. Sumpter. 1997. The estrogenic activity of phthalate esters *in vitro*. *Environ.Health Perspect.* 105(8): 802-811.

Harrison Research Laboratories. 1998. Repeated insult patch test (RIPT) on a nail enamel. Unpublished data submitted by CTFA (13 pages).

Hill Top Research, Inc. 1968. Primary irritation patch test on 3239K. Unpublished data submitted by CTFA (13 pages).

Hill Top Research, Inc. 1971. Repeated insult patch test of group number 69, A-40-DIETPH. Unpublished data submitted by CTFA (11 pages).

Hill Top Research, Inc. 1998. Evaluation of phototoxicity in humans. HTR project no. 101649. Unpublished data submitted by CTFA (56 pages).

Hill Top Research, Inc. 1999. Evaluation of phototoxicity in humans. HTR project no. 100688. Unpublished data submitted by CTFA (62 pages).

Hill Top Research, Ltd. 1997a. Evaluation of human photoallergy by repeated insult patch test. Project no. 97-4182-74. Unpublished data submitted by CTFA (58 pages).

Hill Top Research, Ltd. 1997b. Evaluation of human photoallergy by repeated insult patch test. Project no. 97-4193-74. Unpublished data submitted by CTFA (84 pages).

Hoppin, J. A., J. W. Brock, B. J. Davis, and D. D. Baird. 2002. Reproducibility of urinary phthalate metabolites in first morning urine samples. *Environ. Health Perspect.* 110(5): 515-518.

Houlihan, J., C. Brody, and B. Schwan. 2002. Not too pretty. Phthalates, beauty products & the FDA. Unpublished report released by Environmental Working Group, Coming Clean, and Health Care Without Harm. Available at: http://www.nottoopretty.org

Imajima, T., T. Shono, O. Zakaria, and S. Suita. 1997. Prenatal phthalate causes cryptorchidism postnatally by inducing transabdominal ascent of the testes in fetal rats. *J. Pediatr. Surg*. 32(1): 18-21.

Inveresk Research International. 1990. 2 weeks dermal dose range finding study in rats. Unpublished data submitted by CTFA (652 pages).

Ivy Research Laboratories. 1973. The primary irritation potential of one fragrance material in six different vehicle formulations. Unpublished data submitted by CTFA (5 pages).

Ivy Research Laboratories. 1984. The determination of the contact-sensitizing potential of four materials by means of the maximization study. Unpublished data submitted by CTFA (4 pages).

Jackson Research Associates. 2002. Analysis of the Subungual Penetration of 100% Dibutyl Phthalate (DBP) in Human Fingernails. Unpublished report submitted by the American Beauty Association October 25, 2002.

Japanese Plasticizer Industrial Association. 1997. Evaluation of estrogen activity of phthalate esters by receptor-binding test (Study no.: 6L471). Unpublished data submitted by Phthalate Esters Panel, American Chemistry Council (59 pages).

Japanese Plasticizer Industrial Association. 1998. Evaluation of estrogen activity and mechanism of action of DBP and DEHP by *in vivo* assay using rats (Study no.: 7L432). Unpublished data submitted by Phthalate Esters Panel, American Chemistry Council (27 pages).

Jensen PA, O'Brien D. (1993) Industrial Hygiene. In: Willeke K, Baron PA eds. *Aerosol Measurement. Principles Techniques and Applications*. New York: John Wiley and Sons, Inc., 538-540.

Jones, H. B., D. A. Garside, R. Liu, and J. C. Roberts. 1993. The influence of phthalate esters on Leydig cell structure and function *in vitro* and *in vivo*. *Exp. Molecul. Pathol.* 58: 179-193.

Jury, H. H., T. R. Zacharewski, and G. L. Hammond. 2000. Interaction between human plasma sex hormone-binding globulin and xenobiotic ligands. *J. Steroid Biochem. & Molecular Biology*. 75: 167-176.

Kageyama, K., Y. Onoyama, T. Nakajima, S. Otani, I. Yano, H. Hotta, I. Matsui-Yuasa, H. Kogawa, and N. Miwa. 1994. DNA synthesis inhibition and transmembrane permeation into tumor cells by various dialkyl phthalates upon hyperthermia. *Anticancer Research*. 14: 2769-2772.

Kanerva, L., R. Jolanki, K. Alanko, and T. Estlander. 1999. Patch-test reactions to plastic and glue allergens. *Acta Derm Venereol.* 79: 296-300.

Kanerva, L., R. Jolanki, and T. Esterlander. 1997. Allergic and irritant patch test reactions to plastic and glue allergens. *Contact Dermatitis.* 37: 301-302.

Karmin, M.A. and G. H. Mayor. 1991. Diethyl phthalate: a perspective. *J. Clin. Pharmacol.* 31: 484-489.

Kavlock, R., K. Boekelheide, R. Chapin, M. Cunningham, E. Faustman, P. Foster, M. Golub, R. Henderson, I. Hinberg, R. Little, J. Seed, K. Shea, S. Tabacova, R. Tyl, P. Williams, and T. Zacharewski. NTP Center for the Evaluation of Risks to Human Reproduction: phthalates expert panel report on the reproductive and developmental toxicity of di-*n*-butyl phthalate. *Reproductive Toxocology* 16:489-527.

Khaliq, M. A., M. S. Alam, and S. P. Srivastava. 1992. Implications of physico-chemical factors on the migration of phthalate esters from tubing commonly used for oral/nasal feeding. *Bull Environ Toxicol.* 48: 572-578.

Kim, S. H., S. S. Kim, O. Kwon, K. H. Sohn et al. 2002. Effects of dibutyl phthalate and monobutyl phthalate on cytotoxicity and differentiation in cultured rat embryonic limb bud cells; protection by antioxidants. Toxicol. Environ. Health. 65 (5-6): 461-472.

Kleinsasser, N. H., E. R. Kastenbauer, H. Weissacher, R. K. Muezenrieder, and U. A. Harréus. 2000. Phthalates demonstrate genotoxicity on human mucosa of the upper aerodigestive tract. *Environmental and Molecular Mutagensis.* 35: 9-12.

Kluwe, W.M. 1982. Overview of phthalate ester phamacokinetics in mammalian species. *Environ. Health Perspectives.* 45: 3-10.

Kohn, M.C., F. Parham, S. A. Masten, C. J. Portier, M. D. Shelby, J. W. Brock, and L. L. Needham. 2000. Human exposure estimates for phthalates. *Environ. Health Perspectives.* 108(10): A440-A442.

Koo, J. W., F. Parham, M. C. Kohn, S. A. Masten, J. W. Brock, L. L. Needham, and C. J. Portier. 2002. The association between biomarker-based exposure estimates for phthalates and demographic factors in a human reference population. *Environ. Health Perspect.* 110(4): 405-410.

Kozombo, W. J., R. Kroll, and R. J. Rubin. 1982. Assessment of the mutagenicity of phthalate esters. *Environ. Health Perspect.* 45: 103-109.

Kurata, Y., F. Kidachi, M. Yokoyama, N. Toyota, M. Tsuchitani, and M. Katoh. 1998. Subchronic toxicity of di(2-ethylhexyl) phthalate in common marmosets: Lack of peroxisomal proliferation, testicular atrophy, or pancreatic acinar cell hyperplasia. *Toxicol. Sci.* 42: 49-56.

Lamb, J.C., R. E. Chapin, J. Teague, A. D. Lawton, and J. R. Reel. 1987. Reproductive effects of four phthalic acid esters in the mouse. *Toxicology and Applied Pharmacology.* 88: 255-269.

Lamb, J. C., J. Reel, and A. D. Lawton. 1997a. Diethylphthalate. Environ. Health Perspet. 105(1): 245-246.

Lamb, J. C., J. Reel, and A. D. Lawton. 1997b. Di-n-butylphthalate, Mice. *Environ. Health Perspect.* 105(1): 247-248.

Leberco Laboratories. 1963. Rabbit eye irritation study of 12.5% deithyl phthalate. Unpublished data submitted by CTFA (5 pages).

Lington, A., M. Bird, R. Plutnick, W. Stubblefield, and R. Scala. 1997. Chronic toxicity and carcinogenic evaluation of di-isononylphthalate in rats. *Fundam. Appl. Toxicol.* 36: 79-89.

Lisheng, W., W. Chutse, P. Xuetao et al. 1996a. Dibutyl phthalate purged autologous bone marrow transplant in the treatment of leukemia. *Leukemia Research.* 20(4): 343-348.

Lisheng, W., W. Chutse, P. Xuetao, X. Li, C. Jurong, and H. Fuchu. 1996b. Purging effect of dibutyl phthalate on leukemic cells associated with apoptosis. *Leukemia Research.* 20(11/12): 989-992.

Liss, G. M., P. W. Albro, R. W. Hartle, and W. T. Stringer. 1985. Urine phthalate determinations as an index of occupational exposure to phthalic anhydride and di(2-ethylhexyl)phthalate. *Scand. J. Work Environ. Health.* 11: 381-387.

Lovekamp, T. N. and B. J. Davis. 2001. Mono-(2-ethylhexyl) phthalate suppresses aromatase transcript levels and estrodiol production in cultured rat granulosa cells. *Toxicol. Appl. Pharmacol.* 172: 217-224.

Lygre, H., E. Solheim, and N. R. Gjerdet. 1995. Leaching from denture base materials *in vitro*. *Acta Odontol Scand* 53: 75-80.

McKee, R. H. 2000. The role of inhibition of gap junction intercellular communication in rodent liver tumor induction by phthalates: Review of data on selected phthalates and their potential relevance to man. *Regulatory Toxicol. & Pharmacol.* 32: 51-5.

Melnick, R. L. and C. M. Schiller. 1985. Effect of phthalate esters on energy coupling and succinate oxidation in rat liver mitochondria. *Toxicology* 34: 13-27.

Milligan, S. R., A. V. Balasubramanian, and J. C. Kalita. 1998a. Relative potency of xenobiotic estrogens in an active *in vivo* mammalian assay. *Environ. Health Perspect.* 106(1): 23-26.

Milligan, S.R., O. Khan, and M. Nash. 1998b. Competitive binding of xenobiotic oestrogens to rat alpha-fetoprotein and to sex steroid binding proteins in human and rainbow trout (Oncorhynchus mykiss) plasma. *General and Comparative Endocrinology.* 112: 89-95.

Ministry of Health, Labor and Welfare. 2001a. Unofficial translation of MHW Ordinance No. 331, Attached Table 1 [Negative List]. Ministry of Health, Labor and Welfare, Pharmaceutical and Medical Safety Bureau, Inspection and Guidance Division, 2-2, 1-chome, Kasumgaseki, Chiyoda-ku, Tokyo 100-8045, Japan.

Ministry of Health, Labor and Welfare. 2001b. Unofficial translation of MHW Ordinance No. 331, Attached Table 2 [Restricted List]. Ministry of Health, Labor and Welfare, Pharmaceutical and Medical Safety Bureau, Inspection and Guidance Division, 2-2, 1-chome, Kasumgaseki, Chiyoda-ku, Tokyo 100-8045, Japan.

Mint, A., S. A. M. Hotchkiss, and J. Caldwell. 1994. Percutaneous absorption of diethyl phthalate through rat and human skin *in vitro*. *Toxic. In Vitro.* 8(2): 251-256.

Monsanto Europe. No date. Study to evaluate the effect of monobutyl phthalate on uterine growth in immature female rats after oral administration. Unpublished data submitted by Phthalate Esters Panel, American Chemistry Council (16 pages).

Moura, C., M. Dias, and T. Vale. 1994. Contact dermatitis in painters, polishers and varnishers. *Contact Dermatitis.* 31: 51-52.

Murakami, K., K. Nishiyama, and T. Higuti. 1986a. Mitochondria effect of orally administered dibutyl phthalate in rats. *Japanese Journal of Hygiene.* 41(4): 769-774.

Murakami, K., K. Nishiyama, and T. Higuti. 1986b. Toxicity of dibutyl phthalate and its metabolites in rats. *Japanese Journal of Hygiene.* 41(4): 775-781.

Murature, D. A., S. Y. Tang, G. Steinhardt, and R. C. Dougherty. 1987. Phthalate esters and semen quality parameters. *Biomedical and environmental mass spectrometry.* 14: 473-477.

Mylchreest, E., R. C. Cattley, and P. M. D. Foster. 1998. Male reproductive tract malformations in rats following gestational and lactational exposure to di(n-butyl) phthalate: An androgenic mechanism? *Toxicological Sciences.* 43: 47-60.

Mylchreest, E., M. Sar, R. C. Cattley, and P. M. D. Foster. 1999. Disruption of androgen-regulated male reproductive development by di(n-butyl) phthalate during late gestation in rats is different from flutamide. *Toxicol. and Appl. Pharmacol.* 156: 81-95.

Mylchreest, E., D. G. Wallace, R. C. Cattley, and P. M. D. Foster. 2000. Dose-dependent alterations in androgen-regulated male reproductive development in rats exposed to di(n-butyl) phthalate during late gestation. *Toxicol. Sci.* 55: 143-151.

Mylchreest, E., M. Sar, D. G. Wallace, and P. M. Foster. 2002. Fetal testosterone insufficiency and abnormal proliferation of Leydig cells and gonocytes in rats exposed to di(n-buytl) phthalate. Reprod. Toxicol. 16(1): 19-28.

Nail Manufacturers Council (NMC). 2001. Letter from NMC including ingredient use product type and concentration survey. Unpublished data submitted by NMC of May 7, 2001. (4 pages.)

National Toxicology Program (NTP). 1991. Final report: on the reproductive toxicity of di-n-butyl phthalate (CAS No. 84-72-2) in Sprague-Dawley rats. NTIS Report No. PB92111996.

NTP. 1995a. NTP technical report on toxicity studies of dibutyl phthalate (CAS No. 84-74-2) administered in feed to F344/N rats and B6C3F1 mice. NTIS Report No. PB95232427.

NTP. 1995b. Toxicology and carconigenesis studies of diethylphthalate in F344/n rats and B6C3F$_1$ mice with dermal initiation/promotion study of diethylphthalate and dimethylphthalate in male Swiss (CD-1) mice. Unpublished data submitted by Phthalate Esters Panel, American Chemistry Council (278 pages).

Netherlands Organization for Applied Scientific Research and National Institute of Public health and the Environment. 2001. Risk assessment, dibutylphthalate. Unpublished data submitted by CTFA (183 pages).

Ohtani, H., I. Miura, and Y. Ichikawa. 2000. Effects of dibutyl phthalate as an environmental endocrine disruptor on gonadal sex differentiation of genetic males of the frog Rana rugosa. *Environ. Health Perspect.* 108(12): 1189-1193.

Ow, R. K. K., and S. Amrith. 1997. Ocular prosthetics: use of a tissue conditioner material to modify a stock ocular prosthesis. *Journal of Prosthetic Dentistry.* 78(2): 218-222.

Paganetto, G., F. Campi, K. Varani, A. Piffanelli, G. Giovannini, and P. A. Borea. 2000. Endocrine-distrupting agents on healthy human tissues. *Pharmacol. & Toxicol.* 86: 24-29.

Page, B. D., and G. M. Lacroix. 1992, Studies into the transfer and migration of phthalate esters from aluminum foil-paper laminates to butter and margarine. *Food Additives and Contaminants.* 9(3): 197-212.

Payan, J. P., J. P. Marty, J. P. Fabry, D. Beydon, I. Boudry, E. Ferrari, F. Canel, M. C. Grandclaude, and C. M. Vincent. 2001. *In vivo* and *in vitro* percutaneous absorption of [^{14}C]di-n-butylphthalate in rat. *Drug Meatbol. & Distrib.* 29(6): 843-854.

Peakall, D. B. 1975. Phthalate esters: occurrence and biological effects. Residue Review. 54: 1-41.

Pfordt, J. and E. Bruns-Weller. 1999. Phthalate esters as a group of environmental chemicals with an endocrine disruption potential. Lower Saxony Ministry of Food, Agriculture and Forestry: Hamburg. Unpublished data submitted by the Phthalate Esters Panel, American Chemistry Council (53 pages).

Phthalate Esters Panel, American Chemistry Council. 1982a. Toxicity tests of dibutyl phthalate, dibutyl isophthalate, and dibutyl terephthalate. Unpublished data submitted by the Phthalate Esters Panel, American Chemistry Council (5 pages).

Phthalate Esters Panel, American Chemistry Council. 1982b. 28-day subacute percutaneous toxicity SL: VE-1005-20, SR: TGSE #1037, P75-006. Unpublished data submitted by the Phthalate Esters Panel, American Chemistry Council (10 pages).

Phthalate Esters Panel, American Chemistry Council. 1999. Di-n-butylphthalate (DBP). Unpublished data submitted by the Phthalate Esters Panel, American Chemistry Council (42 pages).

Plasterer, M. R., W. S. Bradshaw, G. M. Booth, M. W. Carter, R. L. Schuler, and B. D. Hardin. 1985. Developmental toxicity of nine selected compounds following prenatal exposure in the mouse: napthalene, p-nitrophenol, sodium selenate, dimethyl phthalate, ethylenethiourea, and four glycol ether derivatives. J. Toxicol. Environ. Health. 15: 25-38.

Proctor & Gamble Co. 1984. Teratogenicity study of E-2426.01 (diethyl phthalate) by dermal application to rabbits with cover letter dated 05/02/94. NTIS Report No. OTS0572465.

Pugh, G., J. Isenberg, L. Kamendulis, L. Clare, W. Brown, A. Lington, D. Ackley, J. Smith, and J. Klaunig. 2000. Effects of di-isononyl phthalate, di-2-ethylhexyl phthalate, and clofibrate in cynomolgus monkeys. *Toxicol Sci.* 56(1): 181-188.

Research Triangle Institute. 1995. The toxicokinetics and metabolism of di-n-butyl phthalate. Unpublished data submitted by CTFA (58 pages).

Research Institute for Fragrance Materials (RIFM). 1984. Acute dermal irritation study. RIFM# 1795. Unpublished data submitted by CTFA (13 pages).

RIFM. 1984. Acute dermal irritation study. RIFM# 3099. Unpublished data submitted by CTFA (13 pages).

Saillenfait, A. M., J. P. Payan, J. P. Fabry et al. 1998. Assessment of the developmental toxicity, metabolism, and placental transfer of di-n-butyl phthalate administered to pregnant rats. *Toxicological Sciences* 45:212-224.

Saillenfaint, A. M., I. Langonné, and B. Leheup. 2001. Effects of mono-n-butyl phthalate on the development of rat embryos: *in vivo* and *in vitro* observations. *Pharmacol. & Toxicol.* 89:104-112.

Schreck, C. E. 1991. Permethrin and dimethyl phthalate as tent fabric treatments against *Aedes aegypti*. *J. Am. Mosquito Control Assn.* 7(4): 533-535.

Sciences International, Inc. 1995. Toxicological profile for diethyl phthalate. Unpublished data submitted by CTFA on August 30, 2002. (3 pages.)

Scientific Committee on Cosmetic Products and Non-Food Products (SCCNFP). 2002. Opinion of the scientific committee on cosmetic products and non-food products intended for consumer concerning diethyl phthalate. Unpublished data submitted by CTFA. (36 pages.)

Scott, R.C., P. H. Dugard, J. D. Ramsey, and C. Rhodes. 1987. *In vitro* absorption of some o-phthalate diesters through human and rat skin. *Environ. Health Perspect.* 74: 223-227.

Selene, C. H., J. Chou, J. Holler, and C. De Rosa. 1998. Minimal risk levels (MRLs) for hazardous substances. *J. Clean Technol., Environ. Toxicol, & Occup. Med.* 7(1): 1-24.

Shultz, V. D., S. Phillips, M. Sar, P. M. D. Foster, and K. W. Gaido. 2001. Altered gene profiles in fetal rats after in utero exposure to di(n-butyl) phthalate. *Toxicol. Sci.* 64: 233-242.

Small, L. D., E. O. Dillingham, and J. Autian. 1973. Tissue distribution and excretion of diethyl phthalate following percutaneous administration to female albino rats. Unpublished data submitted by CTFA (23 pages).

Sonde, V., A. D'souza, R. Tarapore, L. Pereira, M. P. Khare, P. Sinkar, S. Krishnan, and C.V. Rao. 2000. Simultaneous administration of diethylphthalate and ethyl alcohol and its toxicity in male Sprague-Dawley rats. *Toxicology.* 147: 23-31.

Srivastava, S., G. B. Singh, S. P. Srivastava, and P. K. Seth. 1990a. Testicular toxicity of di-n-butyl phthalate in adult rats: effect on marker enzymes of spermatogenesis. *Indian Journal of Experimental Biology.* 28: 67-70.

Srivastava, S. P., S. Srivastava, D. K. Saxena, S. V. Chandra, P. K. Seth. 1990b. Testicular effects of di-n-butyl phthalate (DBP): biochemical and histopathological alterations. *Arch. Toxicol.* 64: 148-152.

Tarvainen, K. 1995. Analysis of patients with allergic patch test reactions to a plastics and glues series. *Contact Dermatitis* 32: 346-351.

Tavares, I. A. and N. D.Vine. 1985. Phthalic acid esters inhibit arachidonate metabolism by rat peritoneal leucocytes. *J. Pharm. Pharmacol.* 37: 67-68.

Tokunaga, H, Y. Ching, T. Uchino and M. Ando. 2001. Studies of diethyl phthalate on in vitro percutaneous permeation. J. Soc. Cosmetic Chem. Japan. 35(4): 312-316.

Unilever. 1999. Diethyl phthalate: assessment for oestrogenic potential. Unpublished data submitted by CTFA (126 pages).

US Environmental Protection Agency. 1994a. Final report, clinical safety evaluation of test article diethyl phthalate control (neat); repeated insult patch test, with cover letter dated 05/09/94 (sanitized). NTIS No. OTS0557311.

US Environmental Protection Agency. 1994b. Final report, clinical safety evaluation of test article diethyl phthalate in repeated insult patch test, with cover letter dated 05/09/94 (sanitized). NTIS No. OTS0557309.

Van Beek. L. 1974. Primary skin irritation and eye irritation tests with a perfume concentrate. Unpublished dtaa submitted by CTFA (9 pages).

Waliszewski, St. M. and G. A. Szymczyński. 1989. Determination of phthalate esters in human semen. *Andrologia.* 229(1): 69-73.

Walseth, F. and O. G. Nilsen. 1984. Phthalate esters: II. Effects of inhaled dibutyl phthalate on cytochrome p-450 mediated metabolism in rat liver and lung. *Arch. Toxicol.* 55: 132-136.

Walseth, F. and O. G. Nilsen. 1986. Phthalate esters: effects of orally administered dibutylphthalate on cytochrome p-450 mediated metabolism in rat liver and lung. *Acta Pharmacol. et Toxicol.* 59:263-269.

White, R.D., D. L. Earnest, and D. E. Carter. 1983. The effect of intestinal esterase inhibition on the *in vivo* absorption and toxicity of di-n-butyl phthalate. *Food and Chemical Toxicology* 21(1):99-101.

Wilkinson, S.M. and M. H. Bech. 1992. Allergic contact dermatitis from dibutyl phthalate, propyl gallate and hydrocortisone in Timodine®. *Contact Dermatitis* 27: 197.

Williams, D. T. and B. J. Blanchfield. 1975 The retention, distribution, excretion, and metabolism of dibutyl phthalate-7-^{14}C in the rat. *Journal Agric Food Chem* 23(5): 854-858.

Wine, R. N., L. H. Li, L. H. Barnes, D. K. Gulati, and R. E. Chapin. 1997. Reproductive toxicity of di-n-butylphthalate in a continuous breeding protocol in Sprague-Dawley rats. *Environ, Health Perspect.* 105(1): 102-107.

Zacharewski, T. R., M. D. Meek, J. H. Clemons, Z. F. Wu., M. R. Fieldon, and J. B. Mathews. 1998. Examination of the *in vitro* and *in vivo* estrogenic activities of eight commercial phthalate esters. *Toxicol Sci.* 46: 282-293.

Zhou, Y., M. Fukuoka, and A. Tanaka. 1990. Mechanism of testicular atrophy induced by di-n-butyl phthalate in rats. Part 3. Changes in the activity of some enzymes in the Sertoli and germ cells, and in the levels of metal ions. *Journal of Applied Toxicology* 10(6): 447-453.