ADMIN

Dibutyl Phthalate

EXPERT PANEL MEETING
March 28-29, 2024

Cosmetic Ingredient Review

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Christina Burnett, MS, Senior Scientific Analyst/Writer, CIR
Jinqiu Zhu, PhD, DABT, ERT, DCST, CIR Toxicologist
Date: March 4, 2024
Subject: Strategy Memo for Dibutyl Phthalate

Following the March 2023 discussion of the draft 2024 Priorities List, CIR received communication from members of the FDA nominating Dibutyl Phthalate to the 2024 Priority List, for cause. At its June 2023 meeting, the Panel agreed to accelerate a re-review on Dibutyl Phthalate. The Panel first published the Final Report of the Safety Assessment of Dibutyl Phthalate, Dimethyl Phthalate, and Diethyl Phthalate in 1985 (identified as *originalreport_Phthalates_*032024 in this packet), and concluded that these ingredients are safe for topical application in the present practices of use and concentration in cosmetics.[1] Upon re-review in 2002, the Panel reaffirmed the original conclusion (*2005RRsum_Phthalates_032024*), as published in 2005.[2] In December 2012, the Panel deliberated on studies separately concerning endocrine disruption and diabetes and Dibutyl Phthalate, Diethyl Phthalate, Dimethyl Phthalate, and Butyl Benzyl Phthalate; however, the Panel chose not to re-open the safety assessment of these ingredients and published their discussion as a re-review summary in 2017 (*2017RRsum_Phthalates_032024*).[3] The minutes from the Panel deliberations for all of these documents are included in this package (*original minutes_Phthalates_032024*).

Since the FDA's request was only for Dibutyl Phthalate, CIR staff initiated an extensive literature search for studies on this ingredient dated 1999 forward. A very large number of studies were discovered. A good portion of the studies that have been reviewed also include Diethyl Phthalate and/or Dimethyl Phthalate. ***Does the Panel want to include these two ingredients in this rereview?****

Many of the studies focus on the potential effects of Dibutyl Phthalate on the endocrine system and reproductive and developmental effects, some looking at the reproductive system and development as a whole, while others look at particular aspects. Several studies use zebrafish (*Danio rerio*) to investigate these effects, for example. CIR staff have not included these kinds of non-mammalian studies into safety assessments in the past, but the Panel recently has expressed the necessity of including alternative methodologies into future assessments. ***Does the Panel have any preferences on how to organize the myriad of studies on endocrine/reproductive and developmental effects (e.g., should the endocrine studies be subheadings in the Developmental and Reproductive Toxicity section and related table, or should these studies be classified in a stand-alone section)? With the zebrafish studies, are there specific methodologies and endpoints that CIR staff should include or exclude in the safety assessments? Does the Panel have any other suggestions for how CIR staff should present the data outside of the standard table format?***

According to 2023 US FDA VCRP data, Dibutyl Phthalate and Dimethyl Phthalate have 0 reported uses (see Table 1).[3] Diethyl Phthalate is reported to be used in 1 body and hand skin care preparation. According to the use survey conducted by the Council in 2023, concentrations of use were not reported for Dibutyl Phthalate and Dimethyl Phthalate.[4] However, Diethyl Phthalate is reported to be used at up to 0.12% in a foot powder and at lower concentrations in baby products, bath preparations, hair preparations, and manicuring preparations. All 3 phthalate ingredients had uses reported to the VCRP in

* Note – Butyl Benzyl Phthalate is not a simple alkyl phthalate, and was reviewed in a separate, stand-alone report published in 1992 and re-reviewed initially in 2007. This ingredient is not under consideration for inclusion with the Dibutyl, Diethyl, and Dimethyl Phthalates.

2001, and concentrations of use in leave-on products were as high as 15% for Dibutyl Phthalate, 11% for Diethyl Phthalate, and 2% for Dimethyl Phthalate.[2]

CIR staff further conducted a search in California Safe Cosmetics Program (CSCP) Product Database.[5] As of February 2024, concentrations of use for Dibutyl Phthalate included 1.5 mg/ml in nail products. Use as a solvent in perfumes was also reported (no concentration was reported). Use for Dimethyl Phthalate is reported in hair care products (no concentration was reported). Numerous entries were recorded for Diethyl Phthalate, including uses in bath products (up to 1%), body washes and soaps (up to 0.79%), hair shampoos (up to 0.40%), and skin care products (up to 0.20 %).

In the European Union (EU), Dibutyl Phthalate is listed in Annex II, list of substances prohibited in cosmetic products. restricted from use in any way under the rules governing cosmetic products.[6] In 2004, the Scientific Committee on Cosmetic Products and Non-Food Products (SCCNFP) determined that Dibutyl Phthalate should not be intentionally added to cosmetic products.[7] Dibutyl Phthalate has been classified as a Category 2 toxic substance to reproduction that "may cause harm to the unborn child." Diethyl Phthalate and Dimethyl Phthalate are not restricted from use in the EU.[6] The SCCNFP determined that the safety profile of Diethyl Phthalate supports its use in cosmetic products at the levels reported to be used during their assessment.[8] This opinion was reaffirmed the following year.[9] No opinions by the EU are available on Dimethyl Phthalate.

In the rereview conducted in 2001, the Panel determined the combined daily exposure level of Dibutyl Phthalate from the concurrent use of four cosmetic product categories, including nail basecoat or polish, hair spray, deodorant, and perfume, to be 9.13 µg/kg/d.[2] In addition, an estimate of approximately 5% absorption of Diethyl Phthalate in human skin was considered to be a conservative estimate of Dibutyl Phthalate absorption. To assess the risk of Dibutyl Phthalate, the Panel calculated the margin of safety (MOS) for this ingredient by dividing the no-observed-adverse-effect level (NOAEL) of 331 mg/kg/d (pregnant rats were feed throughout gestation) by the expected exposure of 9.13 µg/kg/d, yielding an MOS of 36,254. A more conservative NOAEL of 50 mg/kg/d (pregnant rats were exposed by gavage from gestation day 12 to 21) yielded an MOS of 5476.

Tolerable daily intake (TDI) values for phthalates have already been determined. Based on the reduction of fetal testosterone and liver effects, the European Food Safety Authority (EFSA) determined a TDI of 50 µg/kg bw/d for Dibutyl Phthalate and other phthalates, such as di-2-ethylhexyl phthalate and butyl benzyl phthalate. According to the EFSA, these values may be appropriate for the entire European population, including the most susceptible ones.[10] The TDI for Dibutyl Phthalate was based on a lowest-observed-adverse-effect level (LOAEL) at 2 mg/kg bw/d and applying an uncertainty factor of 200. The LOAEL was identified due to the observed reductions in spermatocyte development at postnatal day (PND) 21, as well as mammary gland changes in adult male rat offspring.[11] On the other hand, the reference doses (RfD) established by U.S. Environmental Protection Agency (EPA) for chronic oral exposure are 100 and 800 µg/kg/d for Dibutyl Phthalate and Diethyl Phthalate, respectively.[12] Additionally, the US EPA suggest a lower RfD for the overall phthalates of 20 µg/kg bw/d.

For further consideration, CIR staff have calculated the dermal exposure levels to Diethyl Phthalate from various product categories based on the Council's survey (Table 2). A conservative estimation has been performed based on maximum concentration of use in separate categories. When a product category is not specified in a type of cosmetics exposure, the category with the highest exposure level for that type has been selected for the exposure estimate. For example, shower gel is chosen to represent "o*ther bath preparations*" cosmetics since it can be applied to the entire body.

- $\Sigma_{\text{Sum of each of the separate exposures}}$ = 3.4 mg/d + 0.0001045 mg/d + 0.0000388 mg/d + 0.034 mg/d + 0.044 mg/d + 0.28 mg/d + 0.000166 mg/d + 0.063 mg/d + 1.848 mg/d = 5.67 mg/d

- Body weight (adult) = 60 kg

- Skin absorption[13] = 5.5 % (Absorption of Diethyl Phthalate through human skin reached 3.9±1.2% (mean ±SD, n = 4) of the applied dose over 72 h when the skin was occluded and 4.8±0.7% (mean± SD, n = 3) when the skin was unoccluded)

- NOAEL[14] - 150 mg/kg bw/d (repeated dose toxicity): Diethyl Phthalate was administered in the diet of rat (dose at 0, 0.2, 1.0, and 5% in feed, groups of 15 rats of each sex) for 16 wk.
  - 200 mg/kg bw/d (maternal & developmental toxicity): Diethyl Phthalate was administered in the diet of rats (dose at 0, 0.25, 2.5 and 5% in feed) during gestation days 6 -15 (following OECD Guideline 414 - Prenatal Developmental Toxicity Study).

- 222 mg/kg bw/d (reproductive toxicity): dose at 0 (control) 600, 3000 & 15,000 ppm; approximately 15 wk for male and 17 wk for female parents of the F_0 & F_1 generations (following OECD Guideline 416 – Two Generation Reproduction Toxicity Study)

- $SED_{dermal} = \frac{5.67 \text{ mg/d} \times 5.5\ \%}{60 \text{ kg}} = 0.0052 \text{ mg/kg bw/d}$

$$MoS_{dermal} = \frac{NOAEL_{repeated\ dose}}{SED_{dermal}} = \frac{150 \text{ mg/kg bw/d}}{0.0052 \text{ mg/kg bw/d}} = 28{,}846$$

In light of maximum use concentration reported in California's CSCP Product Database, the calculated MoS is 86,206 for bath products (e.g., 1% in shower gel) and 10,489 for skin care products (e.g., 0.2% in body lotion).

The quantitative systemic risk assessment outlined above utilizes concentration data from the Council's survey on phthalates,[4] and incorporates the methodology previously used by the Panel in their review of Dibutyl Phthalate.[2] Given the current lack of detailed information on the frequency and concentration of use for Dibutyl Phthalate and Dimethyl Phthalate, ***the Panel is being asked whether Diethyl Phthalate should be included in the re-opened safety assessment. If so, the question extends to whether the MOS calculations presented above are deemed useful and relevant for inclusion in the report to assess the overall risk of phthalates. Alternatively, does the Panel prefer to request survey data on additional phthalates and perform further calculations?***

Table 1. Frequency (2023/2001) and concentration (2023/2001) of use according to likely duration and exposure and by product category

	Dibutyl Phthalate				Diethyl Phthalate				Dimethyl Phthalate			
	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	2023[15]	**2001[2]**	**2023[4]**	**2001[2]**	**2023[15]**	**2001[2]**	**2023[4]**	**2001[2]**	**2023[15]**	**2001[2]**	**2023[4]**	**2001[2]**
Totals*	**NR**	**150**	**NR**	**0.0038-15**	**1**	**73**	**0.000048-0.12**	**0.00003-11**	**NR**	**12**	**NR**	**0.00002-2**
summarized by likely duration and exposure												
Duration of Use												
Leave-On	*NR*	*147*	*NR*	*0.0038-15*	*1*	*69*	*0.000048-0.12*	*0.00003-11*	*NR*	*12*	*NR*	*0.00002-2*
Rinse-Off	*NR*	*3*	*NR*	*0.007-2*	*NR*	*1*	*0.000097-0.04*	*0.0002-2*	*NR*	*NR*	*NR*	*0.00002-0.004*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*3*	*0.000055*	*0.008-0.09*	*NR*	*NR*	*NR*	*NR*
Exposure Type*												
Eye Area	NR	NR	NR	NR	NR	NR	NR	0.007-0.07	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	0.0038-0.089	1[b]	42; 5[a]; 2[b]	0.0016-0.021; 0.00034-0.07[a]	0.01-11; 0.0004-0.9[a]; 0.008-1[b]	NR	9	NR	0.00002-2
Incidental Inhalation-Powder	NR	NR	NR	NR	1[b]	5; 2[b]	0.12	0.00003-0.4; 0.008-1[b]	NR	NR	NR	0.00008
Dermal Contact	NR	3	NR	0.0038-0.5	1	72	0.000055-0.12	0.00003-11	NR	NR	NR	0.00008-0.2
Deodorant (underarm)	NR	NR	NR	0.014-0.02[a]	NR	4[a]	NR	0.3-1[a]	NR	NR	NR	0.2[a]
Hair - Non-Coloring	NR	NR	NR	0.0055-0.016	NR	1	0.000048-0.07	0.0008-0.4	NR	11	NR	0.00002-2
Hair-Coloring	NR	NR	NR	0.1	NR	NR	NR	NR	NR	1	NR	NR
Nail	NR	147	NR	0.5-15	NR	NR	0.021	0.1-0.2	NR	NR	NR	NR
Mucous Membrane	NR	3	NR	NR	NR	3	0.000055	0.008-2	NR	NR	NR	0.004
Baby Products	NR	NR	NR	NR	NR	NR	0.1	0.00003-0.05	NR	NR	NR	NR
as reported by product category												
Baby Products												
Baby Shampoos	NR	NR	NR	0.03	NR	NR	NR	0.03				
Baby Lotions/Oils/Powders/Creams	NR	NR	NR	0.00003	NR	NR	0.1	0.00003				
Other Baby Products	NR	NR	NR	0.05	NR	NR	NR	0.05				
Bath Preparations (diluted for use)												
Bath Oils, Tablets, and Salts	NR	1	NR	NR	NR	1	NR	NR				
Bubble Baths	NR	NR	NR	0.06	NR	NR	NR	0.06				
Bath Capsules												
Other Bath Preparations	NR	2	NR	0.008-0.09	NR	2	0.000055	0.008-0.09				
Eye Makeup Preparations												
Eyebrow Pencil	NR	NR	NR	0.007	NR	NR	NR	0.007				
Mascara	NR	NR	NR	0.007-0.07	NR	NR	NR	0.007-0.07				
Other Eye Makeup Preparations	NR	NR	NR	0.07	NR	NR	NR	0.07				
Fragrance Preparations												
Cologne and Toilet Water	NR	24	NR	0.2-2	NR	24	NR	0.2-2				
Perfumes	NR	7	NR	1-11	NR	7	NR	1-11				
Powders (dusting/talcum, excl aftershave talc)	NR	5	NR	NR	NR	5	NR	5				
Sachets	NR	2	NR	NR	NR	2	NR	2				
Other Fragrance Preparation	NR	11	NR	0.01-1; 67-28,000 ppm[c]	NR	11	NR	0.01-1; 67-28,000 ppm[c]				

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	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	2023[15]	**2001[2]**	**2023[4]**	**2001[2]**	**2023[15]**	**2001[2]**	**2023[4]**	**2001[2]**	**2023[15]**	**2001[2]**	**2023[4]**	**2001[2]**
Hair Preparations (non-coloring)												
Hair Conditioner	NR	NR	NR	0.1-0.2	NR	NR	0.000097	0.1-0.2				
Hair Spray (aerosol fixatives)	NR	NR	NR	0.4; 17-1500 ppm[c]	NR	NR	0.0016-0.0034	0.4; 17-1500 ppm[c]	NR	8	NR	0.00002-2
Shampoos (non-coloring)	NR	NR	NR	0.0008-0.2	NR	NR	0.04	0.0008-0.2	NR	NR	NR	0.00002
Tonics, Dressings, and Other Hair Grooming Aids	NR	1	NR	14-220 ppm[c]	NR	1	0.00034-0.07	14-220 ppm[c]				
Other Hair Preparations					NR	NR	0.000048	NR	3	NR	NR	NR
Hair Coloring Preparations												
Hair Color Sprays (aerosol)									1	NR	NR	NR
Makeup Preparations												
Blushers (all types)									NR	NR	NR	0.00008
Face Powders	NR	NR	NR	0.4	NR	NR	NR	0.4	NR	NR	NR	0.00008
Foundations	NR	NR	NR	0.3	NR	NR	NR	0.3	NR	NR	NR	0.005
Other Makeup Preparations	NR	NR	NR	0.0003	NR	NR	NR	0.0003				
Manicuring Preparations (Nail)												
Nail Polish and Enamel	NR	NR	NR	0.1	NR	NR	NR	0.1				
Other Manicuring Preparations	NR	NR	NR	0.2	NR	NR	0.21 (spray)	0.2				
Personal Cleanliness Products												
Bath Soaps and Detergents	NR	NR	NR	2	NR	NR	NR	2	NR	NR	NR	0.004
Deodorants (underarm)	NR	4	NR	0.3-1; 20-3300 ppm[c]	NR	4	NR	0.3-1; 20-3300 ppm[c]	NR	NR	NR	0.2; 33 ppm[c]
Feminine Deodorants	NR	NR	NR	0.4	NR	NR	NR	0.4				
Other Personal Cleanliness Products	NR	NR	NR	1	NR	NR	NR	1				
Shaving Preparations												
Aftershave Lotion	NR	4	NR	0.5-2	NR	4	NR	0.5-2	NR	NR	NR	0.2
Shaving Cream	NR	NR	NR	0.001	NR	NR	NR	0.001				
Other Shaving Preparations	NR	NR	NR	1	NR	NR	NR	1				
Skin Care Preparations												
Cleansing	NR	NR	NR	0.0002	NR	NR	NR	0.0002				
Face and Neck (exc shave)	NR	NR	NR	0.3	NR	NR	NR	0.3				
Body and Hand (exc shave)	NR	2	NR	0.008-0.5; 26-190 ppm[c]	1	2	NR	0.008-0.5; 26-190 ppm[c]				
Foot Powders and Sprays	NR	NR	NR	1	NR	NR	0.12	1				
Night	NR	NR	NR	0.0004	NR	NR	NR	0.0004				
Paste Masks (mud packs)	NR	1	NR	0.1	NR	1	NR	0.1				
Skin Fresheners	NR	4	NR	0.1-0.9	NR	4	NR	0.1-0.9				
Other Skin Care Preparations	NR	5	NR	0.00003-0.9	NR	5	NR	0.00003-0.9				

NR – not reported

*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.

**likely duration and exposure are derived based on product category (see Use Categorization https://www.cir-safety.org/cir-findings)

[a] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.

[b] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories

[c] Concentrations reported by the Nail Manufacturer's Council or data from research of off-the-shelf products.[2]

Table 2. Concentration of Use (2023)[4] and Exposure by FDA Product Category – Diethyl Phthalate

Product Category/Type of cosmetics exposure	Daily Exposure by Product Category* (mg/d)	Maximum Concentration of Use	Daily Exposure Based on the Highest Use Concentration (mg/d)	Note
Baby lotions, oils, and creams	3400 κ	0.1%	3.4	Exposure amount of baby body lotion applied
Other bath preparations	190	0.000055%	0.0001045	Exposure amount of shower gel applied
Hair conditioners	40	0.000097%	0.0000388	
Hair sprays Aerosol Pump spray	5000 γ	 0.0034% 0.0016%	 0.034 0.016	Dermal exposure resulted from Hair sprays use, considering 20% skin contact (from PCPC maximum worst case)
Shampoos (noncoloring)	110	0.04%	0.044	
Tonics, dressings, and other hair grooming aids	400	0.00034-0.07%	0.28	Exposure amount of hair styling products applied
Other hair preparations (noncoloring)	345 #	0.000048%	0.000166	Exposure amount of hair styling products (leave-on) applied
Other manicuring preparation Nail enamel finishing spray	300 #	0.021%	0.063	Exposure amount of nail polish applied
Face and neck products Not spray	1540	0.12%	1.848	Exposure amount of face cream/lotion applied

***** Exposure parameters are retrieved from the SCCS NoG[16]

κ Exposure amount is based on surface area/body weight ratio between baby (0-1 year) and adults at 2.3[16]

γ Exposure amount is provided by CTFA (currently known as PCPC) habits and practices data[4]

Exposure amount is provided by Vermeer Cosmolife[17]

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JULY 25-26, 1983 PANEL MEETING – FIRST PUBLIC REVIEW

Full Panel

The following conclusion of the report was unanimously approved:

"On the basis of the available data, the Panel concludes that Dibutyl Phthalate, Dimethyl Phthalate, and Diethyl Phthalate are safe for topical application in the present practices of use and concentration in cosmetics."

Dr. Hoffman suggested mentioning in the Introduction that this review dose not include the carcinogenic ingredient Di(2-ethylhexyl) Phthalate (DEHP).

Dr. Bergfeld requested the clinical data be expanded in the text of the report, and Dr. Hoffman suggested reference be made to the Russian article L.E. Milkov in the clinical section of the report.

Subject to minor revisions, the document will be announced as a Tentative Report for a 90-day comment period.

JUNE 18-19, 2002 MEETING – FIRST RE-REVIEW

Full Panel

Dr. Belsito said that his Team determined that the available data (summarized in the Draft Report) that have been identified in the published literature since the Panel's Final Report on Dibutyl Phthalate was published in 1985 warrant a decision by the Panel to reopen its original safety assessment.

Dr. Belsito said that the concern at this point relates to the anti-androgen effect of Dibutyl Phthalate, and that the Panel needs to do a thorough risk analysis to determine the extent to which its use in cosmetic products (primarily in nail products) contributes to the potential body load of Dibutyl Phthalate. He added that the Panel needs to examine how cosmetics containing this ingredient are used, what the likely absorption would be, and then do a risk assessment on that.

The Panel voted unanimously in favor of reopening the Final Report on the safety of Dibutyl Phthalate in cosmetics.

Regarding the Panel's deliberations on the Phthalates in Teams, Dr. Andersen recalled discussions of additional data that are under development. He said that it is his expectation that, as the studies are completed, the data will be provided to CIR and incorporated into the next draft (Scientific Literature Review) of the CIR report on Dibutyl, Diethyl, and Dimethyl Phthalates.

NOVEMBER 18-19, 2002 MEETING – DRAFT AMENDED REPORT

Full Panel

At the June 18-19, 2002 Panel meeting, the Panel voted unanimously in favor of reopening the Final Report on the safety of Dibutyl Phthalate, Dimethyl Phthalate, and Diethyl Phthalate in cosmetics. This decision was made after reviewing data that have entered the published literature since the Final Report was published in 1985 with the following conclusion: On the basis of the available data, the Panel concludes that Dibutyl Phthalate, Dimethyl Phthalate, and Diethyl Phthalate are safe for topical application in the present practices of use and concentration in cosmetics.

Dr. Marks said that after discussing the anti-androgen effect of Dibutyl Phthalate in great detail and doing a risk analysis (particularly, a margin of safety evaluation), his Team determined that the Panel's original conclusion on Dibutyl Phthalate, Dimethyl Phthalate, and Diethyl Phthalate should not be changed and, thus, that the Panel's original safety assessment should not be reopened. However, it was agreed that the conclusion should be edited as follows to reflect the current wording of CIR's conclusions: Based on the available information included in this report, the CIR Expert Panel concludes that Dibutyl Phthalate, Dimethyl Phthalate, and Diethyl Phthalate are safe for use in cosmetic products in the present practices of use and concentration.

In light of his Team's decision, Dr. Marks added that there should be a lengthy discussion of all of the new data that have been presented and a statement indicating the basis for reaffirmation of the Panel's original conclusion, taking into consideration the no-effect of Dibutyl Phthalate, in particular, the exposure from cosmetics, and the margin of safety that has been devised. Dr. Marks said that his Team determined that there is a significant margin of safety in relation to reaffirming the Panel's original conclusion.

Dr. Bergfeld gave each Panel member an opportunity to comment.

Dr. Slaga said that the data used for the calculations adds a tremendous margin of safety, without taking into consideration that Dimethyl, Diethyl, and Dibutyl Phthalates have different potencies (i.e., ranging from essentially no activity to active [Dibutyl Phthalate]). Therefore, he added that the total cosmetic exposure is diluted by the potency of these Phthalates, Dibutyl Phthalate being the one for which, chemically (because it is used in nail products), its reaction does not make it available as

much as the calculations would indicate. Dr. Slaga also said that greater exposure is associated with Diethyl Phthalate, but, that its activity is weaker, thereby causing another dilution and resulting in a greater degree of safety.

Dr. Katz said that it is common knowledge at FDA that cosmetics represent one area in which Phthalates are used, and that the issue of Phthalates and exposure, as expressed during an earlier discussion, will be addressed on a broader perspective. Relative to FDA's review of some of the data, she added that FDA has also been unable to find the burden of proof or show that there is now a safety issue regarding the use of Phthalates in cosmetics.

Dr. Katz stated that FDA will review the CIR report on Phthalates in more detail, in an effort to identify any additional information that will be useful in further discussions within the agency.

Rachel Weintraub commented on data provided by Dr. McEwen at yesterday's Team meetings, specifically, the potential levels of Phthalates in humans. She said that there appear to be inherent limitations to this analysis, considering that all of the products that contain Phthalates are not known. Ms. Weintraub added that this is supported by a report provided by Health Care Without Harm, which discloses many other products containing Phthalates that the Panel had not been aware of.

Ms. Weintraub noted that Dr. McEwen's analysis includes a number of products (i.e., hair spray, deodorant, perfume, and nail polish), but does not include others which may contain Phthalates in the fragrances or flavors that are not indicated on the label (e.g., shampoos and body lotions).

Regarding yesterday's Team discussion (Dr. Mark's Team), Ms. Weintraub recalled comments on the additive effects of DBP and DEHP (source: poster by Foster et al.). She stressed the importance of including all of the data discussing the additive effects, rather than use of the poster by Foster et al. only.

Dr. McEwen said that the memorandum to CIR that he completed this morning addresses the aggregate exposure, as presented in a document from Health Care Without Harm, taking the most conservative NOEL and the 95th percentile maximally exposed subset of the population. This includes all DBP exposure, because it is a biomeasurement of that population. Dr. McEwen stated that the memorandum to CIR will be available to the public.

Dr. McEwen expressed industry's appreciation of information on Phthalates from the public. He said that the documents provided (particularly, the study on exposures from various products) helped him arrive at a decision as to the probable human exposure to Phthalates.

Dr. Bergfeld asked if anyone in the audience wished to make a brief statement.

Charlotte Brody, with Health Care Without Harm, expressed disappointment over the fact that her small, non-profit organization, in collaboration with two other small groups, had to present the cosmetics industry with data on Phthalate levels in its own products. She said that there should be more transparency in terms of which products contain Phthalates, and that this information needs to be made available.

Ms. Brody added that it is difficult for her to respond to Dr. McEwen's use of Health Care Without Harm's study, considering that his information was presented this morning. She said that this is not her idea of a public process. Similarly, she expressed disappointment over the fact that, in her opinion, calculations (based on industry's data on exposure) done in Teams yesterday will not be made available to everyone.

Ms. Brody asked the Panel to consider the question of whether or not the population would be better off with less or more Phthalate exposure. She said that the message to industry should be that less Phthalates in cosmetics would be better than more.

The Panel unanimously concluded that the Final Report on Dibutyl Phthalate, Dimethyl Phthalate, and Diethyl Phthalate should not be reopened and that the Panel's original conclusion should not be changed.

In summary, the Panel compared the current uses and consumer exposures with the available safety test data, and concluded that not only are exposures low compared to levels shown to produce adverse effects in animals, but that there was a high margin of safety between exposures and levels demonstrated to produce no-observable-effects in animal tests. Therefore, the Panel concluded that these ingredients are safe for use in cosmetic formulations in the current practices and concentrations of use, and that there was no need to reopen the safety assessment. This conclusion, an extensive presentation of the new scientific studies and other data considered by the Panel, and the rationale for the decision will be included in CIR 's Annual Review, which presents the rationale for decisions not to reopen prior safety assessments.

Dr. Bergfeld asked that the Panel have an opportunity to review the Annual Review prior to its announcement.

Dr. Andersen said that the Annual Review will be made available to the Panel prior to its announcement.

FEBRUARY 6-7, 2003 MEETING – FIRST RE-REVIEW SUMMARY

Full Panel

A CIR Final Report with the following conclusion was published in 1985: On the basis of the available data, the Panel concludes that Dibutyl Phthalate, Dimethyl Phthalate, and Diethyl Phthalate are safe for topical application in the present practices of use and concentration in cosmetics. Since this conclusion was issued, many additional studies have appeared in the scientific literature. These studies, along with current frequency of use and use concentration data, were considered by the CIR Expert Panel.

On November 19, 2002, the CIR Expert Panel announced its decision to not reopen the Final Safety Assessment on the Phthalates and asked that a summary of the newly available data and a discussion of the issues be prepared for the Panel's review.

Dr. Bergfeld stated that the Panel has been provided with the re-review summary and discussion on the Phthalates, to be published in the Annual Review, for review at this Panel meeting.

Dr. Andersen noted that this request was made because of the understanding that documentation of the decision not to reopen (i.e., the summary for inclusion in the Annual Review) the Final Report on Phthalates would be different in comparison with other decisions not to reopen that have been made. He said that this is based on the need to present and discuss a large amount of new information on the Phthalates.

Dr. Andersen also stated that the Panel now has an opportunity to comment on the summary and discussion that have been prepared.

Dr. Snyder said that the Panel's reason for not reopening the Final Report should be stated in the first paragraph of the summary.

In response to Dr. Snyder's comment, Dr. Andersen proposed the following statement: Based on its consideration of the data discussed below, the Panel decided not to reopen this safety assessment.

DECEMBER 10, 2012 MEETING – SECOND RE-REVIEW/STRATEGY MEMO

Dr. Belsito's Team

DR. BELSITO: Right. Exactly. Thank you. Okay. We have time for a few more here. So let's at least start the phthalate discussion. And I guess since Alan is here and he had a chance to review this guidance for industry document and it was just sitting here when I got here and I haven't even seen it yet, basically this came from the FDA Center for Drug Evaluation and Research.

DR. ANDERSEN: That's correct.

DR. BELSITO: So, not from cosmetics.

DR. ANDERSEN: Right.

DR. BELSITO: And their recommendation is in drugs to do what?

DR. ANDERSEN: Phthalates in particular dibutyl phthalate and diethylhexyl phthalate have uses as excipients in drugs, and because there are alternatives to perform those excipient functions at the Center for Drug Evaluation and Research is recommending that the two phthalates not be used. And the science behind it is nothing different than what you have reviewed. There's really no new data. What's different is that the Center for Drugs Evaluation and Research has applied the precautionary principle and not a risk assessment. What you guys have done is a risk assessment with large margins of safety vis a vis cosmetics. So, I would argue that this doesn't have any real impact on the phthalate question, but you needed to know it exists.

DR. BELSITO: Okay.

DR. BRESLAWEC: Dr. Belsito? I might point out that the FDA guidance specifically states that the recommendations in this guidance do not address the use of DBP or DEHB in other types of FDA regulated products.

DR. BELSITO: Well, diethylhexyl phthalate is not a cosmetic ingredient anyway, right? I mean, because we deal with what, dibutyl, diethyl, and --

DR. ANDERSEN: Butyl benzyl.

DR. BELSITO: Butyl benzyl.

DR. ANDERSEN: Yeah, that's correct but I think that sentence in the guidance document was written more for the Center for Devices and Radiological Health, which does have diethylhexyl phthalate as a cross to bear because of its use in tubing to keep it flexible.

DR. BELSITO: Okay. So anyway, what we're presented here were three different studies. One done on a South Bronx population of children looking at phthalates in airway inflammation as measured by nitric oxide, and then two studies looking at diabetic populations. One from Uppsala, Sweden and the other based upon the NHANES data in the United States.

I thought the phthalates and airway inflammation -- I mean, they were able to draw some lines but when I looked at the scattergrams it looked like it was all over the place and I had a real hard time making any sense of it.

The diabetic studies -- I'm not a statistician and I was just sort of overwhelmed with the statistical analysis of these studies, but also impressed that there did seem to be somewhat of a correlation with urinary phthalates and diabetes. And then a possible explanation for this, you know, based upon the nuclear praxisome proliferating activity and the fact that there are drugs that target that to treat diabetes.

So, I don't know if that's cause for re-opening because I'm not sure that phthalates from cosmetic preparations are absorbed to a level where that will reasonably occur. Also, they were looking at phthalates that aren't used in cosmetics, so I really thought that when I was looking at those levels of non-cosmetic phthalates that there were other sources that were likely more important if this was even real, which I'm not sure it is. But there were sources of phthalate exposure such as freezing plastic water bottles or microwaving in plastic whatever that probably were more important than what we were seeing in terms of exposure from cosmetics.

But that was my own personal view, so I open it up to people who know more about phthalates and diabetes and airway inflammation than I do.

DR. SNYDER: Who would that be? (Laughter) Yeah, I read the data on all these. I thought they both did a good bit of addressing the study limitations of both studies. I still think that the big missing link is what's the underlying mechanism. You know, we have these associations but how does that link that they're related, I think is one issue.

I did want to know that we did not have -- I didn't understand why we did not have the Gaithera, 2004 reference was not in our document, in our report previously. But I thought that we had addressed the issues related to -- in the old report we did address the metabolism issues and the enzyme systems as it pertained to the diabetes report. So, I thought we had addressed some of that even though it wasn't directly linked maybe at the time to diabetes, but we were already aware of those issues about the enzyme systems regarding the metabolism of the phthalates.

So, I wasn't all that concerned about the new data set in regards to what we already know about the phthalates.

DR. LIEBLER: I think the papers establish that there is a relationship between the parameters measured and nothing more. I -- you know, for example between exhaled nitric oxide and urinary phthalate metabolites. There is a statistically significant relationship that may or may not be biologically significant, and so I felt that way about all three of these papers. Essentially there are three variations on the same type of study.

And so I said, okay, well if we did use this to re- open what the heck would we do once we did that? Because we can't interpret these studies at any level mechanistically that would inform our evaluation of our prior conclusion. So for that reason I felt that we really can't use these studies to really re-evaluate our conclusion because they provide really no mechanistic insight as to whether or not there's any causal relationship between these ubiquitous environmental contaminants and the disease states -- either airway disease or diabetes.

So I felt if we did re-open it we'd have no place to go and we wouldn't really end up being able to change our conclusion. So for that reason, I suggest we do not re-open.

DR. KLASSEN: I'll basically second what Dan said. You know, these are -- these three studies kind of show a weak association. You know, the data is not that impressive. You know, they are statistical associations. I mean, we know that the -- what the phthalates do biologically, and that's been covered before.

I question that it is a biological significance, or even if it might be reproduce-able in another study. So, there are many explanations for why these associations might occur and to suspect that they really are important is premature at this stage. And I think we should not re-open, because of these papers or anything else.

We also have another paper, I guess, on our desk this morning in regard to the sulfation with the phthalates that we might want to address.

DR. BELSITO: I didn't see that.

DR. KLASSEN: It had to do with sulfation.

DR. BELSITO: Oh, that was part of the child/infant report.

DR. KLASSEN: Yeah, might use it two different ways.

DR. BELSITO: Oh, okay. So we acknowledge the papers, we've read them and don't want to do anything with them. So, Alan, how do we communicate to the public that we did this?

I mean, were we being asked to potentially re-open this on the basis of this data? I thought this was like a panel FYI.

DR. ANDERSEN: Well, it's a panel FYI but you do need to make the decision if the information crosses the threshold to re-open.

DR. BELSITO: Okay.

DR. ANDERSEN: By saying that it doesn't, we'll capture that in the minutes of the meeting and it will become a matter of public record.

DR. BELSITO: Okay.

DR. BERGFELD: But also, it will be in our record and the annual report, will it not? That which we have not re-opened and the reasons given.

SPEAKER: Yes.

DR. BELSITO: I guess the only thing that I have a slight discrepancy with is, you know, when we say, you know, we have no mechanistic clue. I would agree with the airway inflammation but, you know, I thought the argument for the peroxisome proliferator receptors in diabetes was pretty cogent. So, I think they offered a potential mechanism there, so I think we have to come up more with then just a statement we don't think there's any mechanism that helps us.

You know, my point was that they were looking at levels of phthalates that aren't used in cosmetics and in fact the -- as I interpreted the data, the burden from cosmetic use was insignificant compared to burdens from other exposures, particularly given the levels of non-cosmetic phthalates that were found in the urine. So, that was my point. Not that, you know, these were interesting articles. You know, there was an association, there was a potentially plausible explanation for a link. The issue was, we don't think the exposure is largely from cosmetics, we think the cosmetic exposure is negligible and that -- number one, and number two there needs to be further investigations. You know, there were limitations in the study, as the authors readily acknowledge. These studies had limitations, yadda, yadda, yadda.

But to simply say there was no mechanistic explanation for airways, I would agree. But for diabetes, I would have a little bit of a pause.

DR. SNYDER: I agree. I think they did address, and very well -- they said this could potentially be a plausible mechanism, but they even conclude themselves that their data set is insufficient at this time to conclude that that is a mechanism action that further studies are required.

I think it's the same conclusion that we would come up with if they hadn't written that, or that's what we're saying, is that we are aware of these associations but at this time there's no data to support they're nothing more than associations.

DR. BELSITO: I'm sure you can wordsmith it.

DR. ANDERSEN: Message received.

Dr. Marks' Team

DR. MARKS: Okay. Talking about phthalates. So, this morning we found this. The guidance for industry limiting the use of certain phthalates as expediencing CDER regulated products. In 2005, the panel decided not to reopen the phthalates particularly at that time we were focused on the possible endocrine disrupter development issues.

We have some new studies. One, an airway study and a couple on diabetes. Alan's summary states the issues well. Is there any reason to reopen?

DR. SLAGA: Do not reopen.

DR. SHANK: Well, those epidemiological studies are not a cause to reopen. I'm not too sure how to handle this. I haven't read it yet. The CDER regulation but if this applies to drugs is it also going to apply to cosmetics eventually.

DR. ANDERSEN: Very specifically not.

DR. SHANK: Okay.

DR. ANDERSEN: Not the medical devices, not the cosmetics, it's dibutylphthalate, diethylhexophthalate as used as excipients in drugs only.

DR. SHANK: Okay. Thank you.

DR. ANDERSEN: I just didn't want to hide it since it came out last Friday. It seemed timely.

DR. SHANK: Yes. Okay. Then I would say don't reopen.

DR. MARKS: Ron Hill, not reopen? Yeah, okay. Now, in terms of the discussion and the re-review.

DR. SLAGA: Well, we definitely have to discuss the epi studies but as Ron pointed out the early association, there's no way to come up with a concentration to relate to cosmetic. There is concern in my eyes that some of these phthalates may have effect on people who are gamma receptors. Which the gamma ones are the ones that the diabetes drugs, the glitazone class of compounds are effective agonists. And then also the alpha, there's a number of different types of fibrates that interrelate to this too that I just think we just discuss that and that's all we have to do.

DR. ANSELL: Well, this is not a re-review. This was three specific papers which questioned whether this should jump out of cycle.

DR. SLAGA: Yeah.

DR. ANSELL: So, I don't know that, I mean that's of course an issue and we can reopen based on --

DR. SLAGA: No, no. I didn't say reopen. This is in a re-review summary.

DR. ANSELL: But this isn't a re-review, right?

DR. MARKS: It's a thick document for not being a re-review.

DR. ANSELL: I thought this was -- I'm sorry. Maybe I'm out -- I thought this was brought forward specifically to assess three papers that we became aware of.

DR. ANDERSEN: That's correct. It's -- you have the option of reopening based on these new data but the minutes of the meeting could be an adequate summary of the basis --

DR. SLAGA: Right.

DR. ANDERSEN: -- for a decision to not reopen it. Like you did at the last meeting with respect to parabens. You said, sorry Charlie, there's not enough new information here to support reopening it. And our previous conclusion is still okay. And that's what I would -- if you choose not to reopen, that's what I'd do here.

DR. MARKS: Leave the minutes and let it stand and not actually publish a re-review summary.

DR. ANDERSEN: Yeah, I think if we did otherwise we'd be publishing a re-review every time somebody published something.

DR. MARKS: Right.

DR. ANDERSEN: No, thank you.

DR. ANSELL: It would make the threshold to look at a paper that came through so onerous that we might not want to do that.

DR. ANDERSEN: Right. Giving you the option of saying, fiddlesticks, this is important. We'd better reopen this. That is what --

DR. MARKS: And so, in the minutes we'll capture that you've already said that, Alan, and Ron Shank is --

DR. ANDERSEN: Yeah and we'd make the note that it specifically excludes any relevance to cosmetics.

DR. MARKS: Okay. So, we'll not reopen phthalates once again and we'll just capture that in the minutes and the biggest three epidemiologic studies don't warrant reopening. Okay.

Full Panel

DR. BELSITO: This is part of our ongoing surveillance of chemicals that have caught the public's attention in various ways. And this was triggered by two reports, one suggesting a linkage between urinary phthalate monofunctional metabolites and airway inflammation as measured by nitric oxide in children from the South Bronx. It was a rather interesting paper with statistical correlation, but when you looked at the individual points, they were really all over the board. And some of the higher phthalate levels were phthalates that are not used in cosmetics, suggesting that exposures were from sources other than cosmetic exposures. And the mechanism of action was speculated, and the authors actually went through great pains to point out the various limitations to their study and what would need to be done.

Then there were two studies on diabetics, one from Sweden and one part that was taken from the U.S. in the Haney study. And again they linked phthalate levels to diabetes, and they specifically subclassified the types of diabetes depending upon phthalate exposure, hypothesizing in effect on nuclear peroxisome proliferating activity receptors because apparently there are diabetic drugs that act via that mechanism. But again --

DR. SLAGA: Antidiabetic.

DR. BELSITO: Antidiabetic, yes, thank you for the correction. But again, despite the statistical linkages, again many of the phthalates were those that aren't used in cosmetic products. And while we took these under advice for lack of a better word, we didn't really feel a need to reopen the phthalate document because of them.

DR. MARKS: Second.

DR. BERGFELD: So a motion has been made and seconded not to reopen. Any other discussion?

DR. MARKS: Our team wanted to know how we would capture this discussion since phthalates are a hot topic and we felt that the minutes would be adequate.

DR. BERGFELD: Alan, can you respond to that? How this will be recorded? It seems to me we have a mechanism in the annual report that appears in The Journal.

DR. ANDERSEN: I think we have traditionally summarized all decisions to not reopen safety assessments and while we haven't published one recently, they are prepared for inclusion in The Journal. I don't know what our track record is at this point in terms of self-initiated re-reviews. That's what I went through was certainly true for the -- as Dr. Belsito referred to a minute ago -- the 15-year mandated re-reviews. Those for sure are done. It's really the Panel's call as to whether this decision is just captured in the meeting minutes or whether a full re-review summary is prepared for publication. In the most recent example, when the Panel reviewed parabens earlier this year, you did not ask for a re-review summary. You just determined to not reopen it based on the handful of new studies that were available.

Procedurally my concern is a new CIR re-review publication every time a paper comes out; that's procedurally a question. But if that's the Panel's desire, we can go in that direction.

DR. BERGFELD: Jim?

DR. MARKS: As I said, our team felt it could be captured in the minutes. Just precisely for what you said, Alan, is that every time a new study came out if we did a re- review summary, it would just become quite burdensome and probably not add much to the safety of these ingredients.

DR. BERGFELD: I'd like to ask a question. Are the minutes available to the public because this, as Don mentioned, is a hot item now and our response would be important?

DR. ANDERSEN: The answer is yes, they are. The post-meeting announcement that will include all of the details of this discussion will be -- if we follow our current practices and procedures -- be online and available by this Friday. So everybody will have -- any interested party will have ample opportunity to see what we did.

DR. BERGFELD: Don?

DR. BELSITO: I guess the only other comment I would make, and you can take it or leave it, would be that, for instance, if you go in to check CIR status and you were to type phthalate, it would come up with our original report and our re-review. It may also be nice when we've taken a special look, even though we've determined not to reopen, not to issue a report, if you typed in phthalates, when it came up it said "discussed at Panel meeting" -- or something to that effect -- "see minutes." And you can hit on it and it links to the minutes. So someone could look and see not only did we re- review phthalates in whatever year, but in December of 2012 we took a look at these three specific papers and decided that for the reasons reflected in the minutes not to go back and reopen the report.

DR. MARKS: That was a question I was going to ask Kevin. Is this searchable? Will it appear?

DR. ANDERSEN: Speaking on Kevin's behalf, I think the answer is it's searchable if we make the extra effort to make it searchable and if there's nothing automatic about it. But I think given Don's comments, message received.

DR. BERGFELD: I'd like to make a comment. Why is it that we cannot do a document, but just not present it for publication but to present it to the linkage in addition to the minutes? I mean it's not -- it's a one-pager usually that updates with the appropriate references, and you can prepare it for the Website, but not particularly for publication..

DR. MARKS: I guess the minutes really capture it the way Don reviewed it, and if we have three more studies that appear in the next six months and we review those studies again, do we do another page document? Pretty soon it'll become a boilerplate as to these three new studies, these two new studies, these five new studies didn't cause us to reopen. So I think it's captured in the minutes as long as the minutes are searchable as Don suggested. I think that's really important so it'll direct you to the meetings of this discussion right today.

DR. HILL: As long as we know that that key word would result in hitting the post-meeting summary. I mean Kevin will know what's needed there to make that happen. To me that would be sufficient except under a circumstance where we really had the need to put together some sort of a paper. There might be conditions, and I'm not sure this would be one of them, but that's just my opinion.

DR. SNYDER: I have a more general comment. I'm less concerned about what we do with the data, just that we're aware of the data. So I'm curious as to what triggered us to be aware of those three publications. And so do we have or is it so to speak on the radar of a particular writer, parabens, the phthalates, the hot button topics, because I think we need to be kept abreast of the current publications. Now whether they rise to the level that we want to consider a reopening or not, I think we should be not waiting 15 years before we ever look at phthalates or parabens again with it being such a public awareness of those ingredients. And I think we need to -- so I'm more concerned about what are we doing to trigger looking for new data on those ingredients.

DR. BERGFELD: Alan?

DR. ANDERSEN: I wish I could give you a presentation of what triggers that happening. It's in the eye of the beholder with respect to the paraben studies that we looked at earlier this year. It just seemed very obvious that we needed to look at that. So it's really between me and the rest of CIR staff flagging that something is important to bring forward. I don't have anything more than we know it when we see it.

DR. BELSITO: And I think that we need to be vigilant in our own various worlds. I mean I get -- a lot of the phthalate issues get directed to Dan and me because we now sit on the RIFM Panel and phthalates are obviously very important to the fragrance industry. And I think -- and then as a dermatologist I have various links that come up to issues related to concerns of chemicals that are in derm products, and paraben is the largest or is the most frequently used preservative in cosmetics. So I think we all need to take our own level of expertise. I'm sure we're all on various Web links that send us information important to what we do. And when we see something coming across about a cosmetic ingredient, we head it back to Alan.

DR. BERGFELD: Halyna, can you respond to how the Council might identify these particular hot button items?

DR. BRESLAWEC: Well, as you can all imagine, we monitor the safety information and concerns about all cosmetic ingredients pretty vigorously. A lot of times it's something we pick up in the press and we decide needs to come to CIR. We've asked CIR for review and opinion. A lot of times our CIR Science and Support Committee will bring something to the table and also the SRTC, the top toxicologists from all the companies who meet on a regular basis, will bring something up. So we've made a practice of bringing articles and issues that raise concerns about ingredients that CIR has reviewed. We make a practice of bringing that to CIR for their review and assessment.

DR. BERGFELD: So basically you're the alert person for us officially?

DR. BRESLAWEC: From our perspective, absolutely, but I just historically know that FDA's done this and that individual members of the Panel have also raised concerns.

DR. BERGFELD: Don?

DR. BELSITO: And the other Website that I follow to find out the latest breaking news, whether it be Internet roar or a scientific publication, is the Environmental Working Group because you can ensure that it pops up very quickly on their site if there are any concerns about cosmetic products..

DR. BERGFELD: Dan?

DR. LIEBLER: One practical point about having, for example, phthalates, this instance of our discussion of phthalates to show up on the Website. But I don't think we necessarily need is for every time phthalates gets mentioned in a transcript incidentally, for example, to pop up in a search. But more along the lines of perhaps the threshold would be if it's on the agenda, there should be an entry and that will probably cover all of these instances then.

DR. ANDERSEN: Well I'm glad you said that because that increases the likelihood that Kevin won't shoot me.

DR. LIEBLER: Especially because I'm right between you and Kevin.

DR. ANDERSEN: But I should -- we've had a lot of discussion about who is watching what's going on in the scientific literature, and I think any interested party should feel empowered to let CIR know if something has appeared that deserves CIR's attention. There's just no reason for there to be any barrier to that happening. So yes, we're vigilant, and we have people who have a self-interest in being vigilant. We have the scientific expertise on the Panel that picks stuff up. All that's great, but anybody ought to be able to raise a red flag and have us pay attention to it.

DR. BERGFELD: We think that we need to vote on this. I'm just surveying if we voted. The conversation went on so long here. But I call for the motion. The motion I believe is not to reopen and to add -- and the discussion led to how we were going to record and link why we did not reopen for the public and our own interest. So if there's no more discussion, let me call for the vote not to reopen. Unanimous. Thank you.

MARCH 18-19, 2013 PANEL MEETING – SECOND RE-REVIEW SUMMARY

Full Panel

Dr. Bergfeld was very pleased with the summary and discussion, and noted that this report sets the precedent for creating this type of document for controversial ingredients that are considered for re-review in the future. She added that the Panel should routinely have an opportunity to review all re-review summaries and discussions before they are published in the Annual Review.

Dr. Andersen said that the re-review summaries could be routinely included on the meeting agenda, for the Panel's comments, prior to publication in the Annual Review. He noted that the public already has an opportunity to comment on these summaries, because the Panel's re-review decisions are announced to the public and a 90-day comment period is observed.

The re-review summary and discussion on Dibutyl Phthalate, Diethyl Phthalate, and Dimethyl Phthalate were approved by the Panel, and Dr. Andersen noted that the announcement of this decision will be followed by a 90-day public comment period.

JUNE 12-13, 2023 – 2024 PRIORITY LIST

Belsito's Team

DR. BELSITO: Priorities. So basically, we've just been asked to prioritize -- that's in admin, right?

DR. SNYDER: Yeah.

DR. KLAASSEN: Yes.

DR. BELSITO: So, since our March meeting we received communication from the FDA nominating ingredients for cause, specifically Toluene and Dibutyl Phthalate. So, we're going to be doing accelerated re-reviews on those. And then there was something here that I just want Monice or someone to clarify. So, it basically said that instead of just doing a re-review summary, we're going to fully open this or something?

MS. FIUME: So, are you talking about Toluene?

DR. BELSITO: Yeah.

DR. SNYDER: We never reviewed it before.

MS. FIUME: Well, it is on our list of items to be re-reviewed. It's currently on Christina's docket. Right, you have Toluene?

DR. BELSITO: Right. We reviewed both of them before.

MS. BURNETT: I think so. I don't know.

DR. SNYDER: Oh, that's the TPO. I was talking about TPO. Yeah.

DR. BELSITO: Right.

DR. SNYDER: I'm sorry, TPO is what I was talking about.

MS. FIUME: Right. TPO is the only on. Dibutyl Phthalate was just re-reviewed in 2017.

DR. BELSITO: Right.

MS. FIUME: But Toluene was scheduled for consideration for re-review this year, so you will be seeing that soon.

DR. BELSITO: Right. But it says, "The CIR will present the panel with a draft amended report on this ingredient instead of an abbreviated re-review document."

MS. FIUME: Okay. So instead of getting the table that you have been --

DR. BELSITO: Right. We are actually going to get a written document?

MS. FIUME: Assuming that you were going to accept FDA's request to reopen it.

DR. BELSITO: I think if FDA comes to us with a request for cause, we have to -- I don't know -- yeah.

MS. FIUME: Which is why you'll get an actual report person versus do you want to reopen? Here's the table of data that we found and then -- just taking that step out.

DR. BELSITO: Right, okay. So, we're going to -- yes, we're reopening Dibutyl Phthalate and Toluene for cause. And I think the third ingredient -- I mean, this is the type of stuff that I want to see happening. Something's going on in Europe, there's a

concern about this material for reproductive toxicity, we need to be looking at it, number one. Number two, we've never even reviewed it. So, yes, I personally would like it added to the 2024 priority list.

DR. SNYDER: Agreed.

DR. KLAASSEN: It would be interesting to know why they wanted these first two chemicals. We don't -- why they want us to do Dibutyl Phthalate?

DR. BELSITO: Because it's a huge issue in endocrine disruption --

DR. KLAASSEN: Right, right.

DR. BELSITO: -- and --

DR. KLAASSEN: But I don't think there's any new data since the last time we did it, but maybe there is. And how about Toluene? I mean, I'm not against doing it, I'm just wondering. It'd be nice if they said why.

MS. FIUME: So, I'm looking at the memo and the email that was originally sent on March 20th, it's PDF Page 26. It just says that they're proposing it.

DR. BELSITO: Yeah. This is from Prashiela.

DR. KLAASSEN: Yeah. It says nothing really.

DR. BELSITO: Right.

MS. FIUME: Sorry, Priya has Toluene. So, Priya will be bringing that back probably in September.

MS. BURNETT: And Phthalates.

MS. FIUME: Yeah.

DR. BELSITO: I mean, both of them have gotten a lot of press, you know, bad press.

DR. KLAASSEN: Yeah, I know about the phthalates always do.

DR. BELSITO: Well, Toluene for carcinogenicity.

DR. RETTIE: So, the phthalates are the less (inaudible) issues, right?

DR. BELSITO: Right. I'm surprised that they are supposedly only one reported use because they used to be used in a lot of nail enamels. But I guess now everyone's using acrylic, so I don't know.

DR. KLAASSEN: Well, let's do them.

DR. SNYDER: Been there, done that.

DR. BELSITO: They're also used in a lot of fragranced products to hold the fragrance on the skin as a fixative, I think.

MS. KOWCZ: No.

DR. BELSITO: No?

MS. EISENMANN: Diethyl.

MS. KOWCZ: The Diethyl.

DR. BELSITO: Yeah, diethyl. Okay.

Cohen's Team

DR. COHEN: All right. Now we're going to Priorities. Okay, for the 2024, draft priorities, we asked for propolis to be accelerated. Two other ingredients were initially proposed and were removed from the list and it was determined that cannabidiol should be reviewed singly.

The others are listed here, some with pretty high frequencies of use reported. Any comments on this? I mean, I don't know if we're going to have a really in depth conversation about this, are we?

DR. HELDRETH: I think that the main point was that FDA had actually asked for three additions to our prioritization. Two of these are request for accelerated rereviews, so Toluene and the Dibutyl Phthalate.

Now Toluene was actually already in our in-house pipeline. We were already working on it, so that one's definitely coming back your way. Dibutyl Phthalate, we haven't started working on yet. But now that FDA has requested it, we've went ahead and added it, unless the Panel has an objection to accelerating that be reviewed.

So, the only real question, I think, for the panel is do they want to add this Trimethybenzoyl Diphenylphosphine Oxide to the prioritization list for next year?

DR. SLAGA: I think we should accelerate it.

DR. COHEN: Yeah. That's a question to the Panel. We should add them.

DR. TILTON: Yeah, I agree.

DR. ROSS: New data. I agree.

DR. HELDRETH: Okay. That's easy.

DR. ROSS: Bart, could I ask you, what was the reason for -- or maybe you don't know -- why FDA nominated Toluene and the Dibutyl Phthalate? Was there a specific reason?

DR. HELDRETH: Prashiela stepped out?

DR. ANSELL: Our FDA person just --

DR. COHEN: We can ask her when she comes back.

DR. ROSS: Ah, okay.

DR. COHEN: These are plastics, the phthalates, right?

DR. HELDRETH: Plasticizer, yeah.

DR. ROSS: Yeah, they're phthalates. Toluene is a little different.

DR. COHEN: Yeah, Toluene is going to be a bit different.

DR. HELDRETH: Well, we've looked at the phthalates before.

DR. ROSS: Yeah.

DR. BERGFELD: And there's a lot of endocrine disruption with that group.

DR. COHEN: So, it's interesting. In 2017, the panel reaffirmed it, so this would be a real short cycle.

DR. HELDRETH: Right.

DR. COHEN: Prashiela, a question. No, no, no, it's okay. For the priority list, the FDA nominated some items, one was Toluene. Do you know why Toluene was nominated?

DR. MANGA: I'm going to have to get back to you on that one. Let me take a quick look at what we --

DR. COHEN: And the phthalates, the dibutyl phthalate?

DR. MANGA: I think there's just a lot of interest in phthalates right now. It's come up quite a bit. The Toluene is being used in a lot of nail products.

DR. ANSELL: Historically.

DR. MANGA: Historically.

DR. COHEN: Are you talking about the Toluene sulfonamide resins or just Toluene?

DR. ANSELL: No Toluene is a diluent.

DR. ROSS: I think Toluene is being reviewed quite a bit at IARC on its own, but also in connection with Benzine.

DR. ANSELL: Right. Also not used anymore, so.

DR. ROSS: Yes.

DR. ANSELL: But we fully support accelerating anything FDA ask us to.

DR. COHEN: We're good. Yeah. So are we.

DR. HELDRETH: Which is a question, I just wondered why they --

DR. BERGFELD: Actually, we really like it when they ask.

DR. ANSELL: Yes. More than support it, encourage it.

DR. MANGA: We appreciate that.

DR. COHEN: No, it's nice we're being paid attention to. And the other one was -- Annex 3 was a little more self-explanatory.

DR. BERGFELD: What was that?

DR. COHEN: The Trimethybenzoyl Diphenylphosphine Oxide.

DR. ROSS: Yeah it's more data. Yeah.

DR. HELDRETH: Yeah, it looks like there may be some repro concerns with that one.

DR. COHEN: Some? I didn't hear what you said.

DR. HELDRETH: Repro -- DART issues with that ingredient.

DR. COHEN: Repro. Okay. All right, so I think we're aligned on the priorities.

DR. BERGFELD: I think when we present this, it would be nice if you, the FDA, presented the reasons for bringing them forth.

DR. COHEN: Just like a sentence.

DR. BERGFELD: It would be very nice.

Full Panel

DR. BELSITO: So the FDA has asked us to move Toluene and Phthalates up for cause. And I would agree with doing that. And also, it was brought to our attention that a material that we haven't reviewed, trimethylbenzoyl dimethyl phosphine oxide, is being looked at by the European Chemical Agency, ECHA. And they're very concerned about the safety of this. It's a substance of very high concern (SVHC), and I think we should move that up on our Priority List as well.

And I think this is the type of thing that needs to be done, where we're monitoring what other safety organizations are looking at, perhaps, flagging ingredients that we weren't aware of. And we should continue to do this type of thing.

DR. BERGFELD: Any comments, Dr. Cohen?

DR. COHEN: No, I thought we might had heard from the FDA a little more why they were nominated.

DR. BERGFELD: Jan, do you want to talk about the nominations?

DR. HELDRETH: We also have Dr. Manga online.

DR. BERGFELD: Manga too?

DR. HELDRETH: She had to return to the office.

DR. MANGA: Hi, this is Prashiela. So these three ingredients came up because we've had a couple of inquiries about these being used in nails -- I'm sorry, I'm getting a bit of feedback from the room.

DR. BERGFELD: We can hear you.

DR. MANGA: So these ingredients have been noted particularly for the use in nail products. And that was why we were interested. And then, as Don mentioned, at least for the TPO, that is coming up as a new ingredient. We were concerned that it be reviewed given the other reviews that are going on.

Toluene is now one of the California Department of Toxic Substances Control products that effective January 1, 2023, nail products containing Toluene will become priority products. And, so, we felt that this was also one that needed to be looked at once again.

In terms of Dibutyl Phthalate, this is one which was included when FDA amended the food-additive regulations, to no longer provide for 25 plasticizers in various foods contact applications. They did this because the uses were abandoned, but given that this one was included in these amendments, we felt that it would be timely for CIR to review it as well.

DR. BERGFELD: Thank you very much. We're really appreciative of the FDA coming in and suggesting these particular ingredients.

JOURNAL OF THE AMERICAN COLLEGE OF TOXICOLOGY
Volume 4, Number 3, 1985
Mary Ann Liebert, Inc., Publishers

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Final Report on the Safety Assessment of Dibutyl Phthalate, Dimethyl Phthalate, and Diethyl Phthalate

Dibutyl Phthalate (DBP), Dimethyl Phthalate (DMP), and Diethyl Phthalate (DEP) are dialkyl phthalates used primarily in cosmetics at concentrations of less than 10 percent as plasticizers, solvents, and perfume fixatives.

These phthalates are rapidly absorbed, metabolized, and excreted. Acute animal feeding studies indicate that these ingredients are nontoxic. The results of most subchronic and chronic tests indicate that these ingredients are relatively nontoxic to rats. The oral administration of DBP produced testicular atrophy in various test rodents. The available data are not adequate to prove that these ingredients are teratogenic agents to experimental animals. This was not observed after the administration of DMP and DEP. Undiluted DBP, DMP, and DEP produced only minimal irritation to eyes of rabbits.

The mutagenic activity of DBP, DMP, and DEP toward *Salmonella typhimurium* mutants is essentially negative, but some assays reported positive findings. Carcinogenesis was not observed in DBP feeding studies.

Limited clinical data on DBP, DMP, and DEP indicate that these ingredients are not human skin irritants, sensitizers, or phototoxic agents. On the basis of the available data, it is concluded that these compounds are safe for topical application in the present practices of use and concentration in cosmetics.

INTRODUCTION

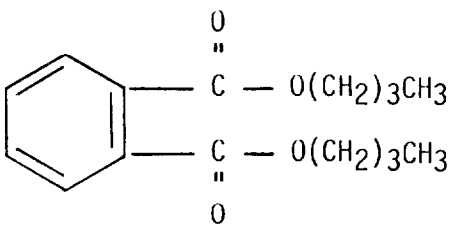
This report reviews the published information and unpublished data supplied by the cosmetic industry on Dibutyl Phthalate, Dimethyl Phthalate, and Diethyl Phthalate. Di(2-ethylhexyl)phthalate, a compound currently of great concern, is not used in cosmetics.

CHEMICAL AND PHYSICAL PROPERTIES

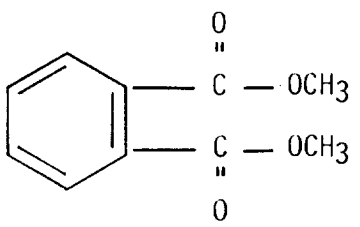
Structure

Dibutyl Phthalate (CAS No. 84-74-2) (DBP), Dimethyl Phthalate (CAS No. 131-11-3) (DMP), and Diethyl Phthalate (CAS No. 84-66-2) (DEP) are dialkyl phthalates. DBP, DMP, and DEP are the aromatic diesters of butyl, methyl, and ethyl alcohol, respectively, and phthalic acid. The chemical formulas of these alkyl phthalates are as follows[1]:

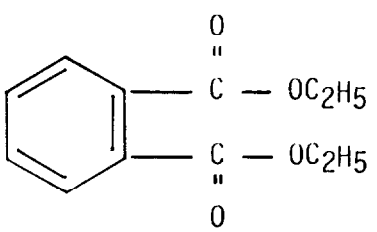
Dibutyl Phthalate



Dimethyl Phthalate



Diethyl Phthalate



Properties

DBP, DMP, and DEP are colorless, oily liquids, soluble in alcohol, ether, and other common organic solvents and almost insoluble in water. DMP is insoluble in petroleum ether and other paraffin hydrocarbons. DBP is odorless. DMP and DEP have no to slight odors, and DEP has a bitter, disagreeable taste.[2-7] DBP is soluble in a solution simulating human sweat (an aqueous solution containing 2.5 g sodium phosphate, 0.2 g triolein, and 2 drops Tween 85/1), and its solubility in this solution increases with an increase in pH.[8] Chemical and properties of DBP, DMP, and DEP are presented in Table 1.

TABLE 1. Chemical and Physical Properties

Property	*DBP*	*DMP*	*DEP*	*Reference*
Molecular weight	278.34	194.19	222.23	
Specific gravity at:				
14/4°C			1.232	7
15.6/15.6°C		1.196		7
20°C	1.0459, 1.0465			7
20/20°C		1.940		7
20/20°C	1.047, 1.049			2
20/20°C		~1.19		3
20/20°C			~1.12	4
20/20°C	1.0484			6
25/25°C		1.189	1.120	6
25/25°C		1.189		7
Boiling point (°C) at:				
760 mm Hg		283.7		7
400 mm Hg		257.8		7
200 mm Hg		232.7		7
100 mm Hg		210.0		7
60 mm Hg		194.0		7
40 mm Hg		182.8		7
20 mm Hg		164.0		7
10 mm Hg		147.6		7
5 mm Hg		131.8		7
1.0 mm Hg		100.3		7
Not specified	340	282	295	5
Not specified	340.0	282	298	6
Not specified	340		295	7
Melting point (°C)				
	−35		−40.5	6
		5.5		7
Vapor pressure (mm Hg) at:				
20°C		<0.1		6
20°C		<0.01		7
150°C	1.1			6
163°C			14	6
182°C			30	6
295°C			734	6
Refractive index at:				
14°C			1.5049	7
20°C	1.4900	1.5168		7
25°C	1.4915	1.5138	1.5002	6

Reactivity

The alkaline hydrolysis products of phthalate esters are mono- and diacids. The second-order alkaline hydrolysis rate constants in water at 30°C are 1.0×10^{-2}, 6.9×10^{-2}, and 2.5×10^{-2} M^{-1} sec^{1} for DBP, DMP, and DEP, respectively. Acid hydrolysis is generally slower than alkaline hydrolysis, and neutral hydrolysis is generally too slow to be detected.[9] DBP is stable in solutions with a near neutral pH.[2]

The products of the thermal decomposition at 250 to 500°C of DBP are 1-butene, butanol, phthalic anhydride, and small amounts of benzoic acid, butyl

benzoate, phthalic acid, and monobutyl phthalate.[10] The major products in the pyrolysis at 730°C of DBP are isobutene, butene, and propylene.[11]

DBP can be degraded by radiolysis. The major product of a 1 ppm aqueous DBP solution at pH 7 after a dose of 3×10^4 rad of gamma radiation is monobutyl phthalate.[12]

Methods of Manufacture and Impurities

Phthalate esters can be prepared by the reaction of phthalic acid with alcohol. DBP, DMP, and DEP are produced industrially by the reaction of phthalic anhydride with butyl alcohol, methyl alcohol, and ethyl alcohol, respectively.[6,7,13] DBP is manufactured by the esterification of phthalic anhydride with an excess of *n*-butyl alcohol. Vacuum stripping removes the unreacted *n*-butyl alcohol. Steam sparging ensures low odor. The phthalate is alkali refined to give a low acid number and is filtered to produce a clear product.[2] The exact manufacturing processes for DMP and DEP are proprietary information. DEP may contain DMP or ethyl methyl phthalate as impurities.[3,4]

DMP and DEP, for use in cosmetics, should contain minimums of 99 percent DMP and DEP, respectively, as determined by gas–liquid chromatography.[2-4,14,15]

Analytical Methods

Qualitative and quantitative determinations of the phthalate esters are made by gravimetric procedures,[15-17] titrimetric analysis,[15] spectrophotometric methods,[18,19] spectrophotofluorometric analysis,[20] the isotope dilution technique,[21] thin-layer chromatography,[22,23] liquid chromatography,[16] liquid chromatography–mass spectrometry,[24] high-performance liquid chromatography,[25,26] gas–liquid chromatography,[3,4,27,28] gas chromatography,[25,29,30] gas chromatography–mass spectrometry,[31,32] high-resolution mass spectrometry, mass fragmentography,[32] gas chromatography with flame ionization,[25] vibration spectroscopy,[33] IR spectroscopy,[14,16,17,34,35] UV spectroscopy,[25,35,36] and NMR spectroscopy.[34,35]

USE

Purpose in Cosmetics

DBP is used in cosmetics as a perfume solvent and fixative, as a suspension agent for solids in aerosols, as a lubricant for aerosol valves, as an antifoamer, as a skin emollient, and as a plasticizer in nail polish, fingernail elongators, and hair spray. DMP is used as a solvent, particularly for artificial musk, and as a plasticizer in fingernail elongators. DEP is used as a solvent for cellulose acetate in nail polish and dopes, as a fixative for perfume, as an alcohol denaturant in toilet preparations, and as a plasticizer in fingernail elongators.[2-5,17,37]

Scope and Extent of Use in Cosmetics

Product types and the number of product formulations containing DBP,

DMP, or DEP and reported voluntarily to the Food and Drug Administration (FDA) in 1981 are presented in Table 2. Voluntary filing of this information by cosmetic manufacturers, packagers, and distributors conforms to the prescribed format of preset concentration ranges and product types as described in the Code of Federal Regulations (21 CFR 720.4)[38] Some cosmetic ingredients are supplied by the manufacturer at less than 100 percent concentration, and, therefore, the value reported by the cosmetic formulator or manufacturer may not necessarily reflect the true concentration of the finished product; the actual concentration in such a case would be a fraction of that reported to the FDA. The fact that data are only submitted within the framework of preset concentration ranges also provides the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same as one entered at the highest end of that range, thus introducing the possibility of a two- to ten-fold error in the assumed ingredient concentration. In 1981, DBP was reported as an ingredient in a total of 590 cosmetic formulations at concentrations ranging from ≤ 0.1 percent to between 10 and 25 percent. DMP was reported as an ingredient in 11 cosmetic formulations at concentrations ranging from ≤ 0.1 percent to between 10 and 25 percent. DEP was reported as an ingredient in 67 cosmetic formulations at concentrations ranging from ≤ 0.1 percent to between 25 and 50 percent.[39]

Surfaces to which Commonly Applied

Cosmetic products containing DBP, DMP, or DEP may be applied to or come in contact with skin, eyes, hair, nails, mucous membranes, and respiratory epithelium (Table 2).[39]

Frequency and Duration of Application

Product formulations containing DBP, DMP, or DEP may be applied as many as several times a day and may remain in contact with the skin for variable periods following application. Daily or occasional use may extend over many years (Table 2).[39]

Potential Interactions with Other Cosmetic Ingredients

No interactions of DBP, DMP, or DEP with other cosmetic ingredients are reported. In typical formulations, the compounds are stable.[2-4]

Noncosmetic Uses

DBP, DMP, and DEP are used as solvents and plasticizers for nitrocellulose, cellulose acetate, and cellulose acetate-butyrate compositions. They are used in the manufacture of varnishes and plastics and in insecticides and insect repellents. DBP is used as a plasticizer in explosives and elastomers, such as polyvinyl, as a textile lubricating agent, as a resin solvent, and in safety glass, printing inks, paper coatings, and adhesives. DMP is used as a camphor substitute in the manufacture of celluloid, as a wetting agent, and as an alcohol denaturant.[6,7]

DBP, DMP, and DEP may be used, at no specific concentration limits, in adhesives used as components of articles intended for packaging, transporting, or holding food (21 CFR 175.105).[38] DBP may be used as a catalyst and crosslinking

TABLE 2. Product Formulation Data[39]

Product Category	Total No. of Formulations in Category	Total No. Containing Ingredient	No. of Product Formulations within Each Concentration Range (percent)					
			>25–50	>10–25	>5–10	>1–5	>0.1–1	≤0.1
Dibutyl Phthalate								
Other hair preparations (noncoloring)	177	3	–	–	–	–	3	–
Other hair coloring preparations	49	3	–	–	–	–	3	–
Other makeup preparations (not eye)	530	1	–	–	–	–	1	–
Nail basecoats and undercoats	44	36	–	–	8	28	–	–
Nail polish and enamel	767	522	–	3	61	168	127	163
Nail polish and enamel remover	41	3	–	1	–	1	1	–
Other manicuring preparations	50	14	–	1	2	9	–	2
Other personal cleanliness products	227	5	–	–	–	5	–	–
Aftershave lotions	282	3	–	–	–	–	3	–
1981 TOTALS		590	–	5	71	211	138	165
Dimethyl Phthalate								
Hair conditioners	478	2	–	–	–	–	2	–
Tonics, dressings, and other hair grooming aids	290	2	–	–	–	1	1	–
Wave sets	180	2	–	–	–	–	2	–
Other hair preparations (noncoloring)	177	4	–	–	–	–	4	–
Hair rinses (coloring)	76	1	–	–	–	–	1	–
1981 TOTALS		11	–	–	–	1	10	–

Diethyl Phthalate								
Bath oils, tablets, and salts	237	3	–	–	–	1	–	2
Other bath preparations	132	2	–	–	–	–	–	2
Eye shadow	2582	1	–	–	–	–	–	1
Colognes and toilet waters	1120	19	–	–	–	1	10	8
Perfumes	657	23	1	–	–	1	7	14
Fragrance powders (dusting and talcum, excluding aftershave talc)	483	1	–	–	–	–	1	–
Sachets	119	3	–	–	–	1	2	–
Other fragrance preparations	191	2	1	–	–	–	1	–
Hair sprays (aerosol fixatives)	265	5	–	–	–	2	3	–
Wave sets	180	1	–	–	–	–	1	–
Nail polish and enamel remover	41	1	–	–	–	1	–	–
Bath soaps and detergents	148	1	–	–	–	–	1	–
Aftershave lotions	282	3	–	–	–	–	3	–
Face, body, and hand skin care preparations (excluding shaving preparations)	832	1	–	–	–	–	–	1
Other skin care preparations	349	1	–	–	–	–	1	–
1981 TOTALS		67	2	–	–	7	30	28

agent for epoxy resins, and DEP may be used as a plasticizer, at no specific concentration limits, in the resinous and polymeric coatings of the food-contact surface of articles intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food. DBP may be used in coatings of containers having a capacity of ≥1000 gallons and intended for repeated use with alcoholic beverages of less than or equal to 8 percent alcohol by volume (21 CFR 175.300, 175.320).[38] There are no concentration limits for the use of DBP as a component of the uncoated or coated food-contact surface of paper and paperboard intended for use in producing, manufacturing, packaging, processing, preparing, treating, packing, transporting, or holding aqueous and fatty foods (21 CFR 176.170).[38] DBP may be used in the base sheet or coating of cellophane used in packaging food, but total phthalates must not exceed 5 percent by weight of the finished cellophane (21 CFR 177.1200).[38] DBP and DMP may be used, at no specific concentration limits, as solvents for inhibitors, accelerators, and catalysts in crosslinked polyester resins used as articles or components of articles intended for repeated use in contact with food (21 CFR 177.2420).[38] DBP may be used as a plasticizer in rubber articles intended for repeated use in producing, manufacturing, packing, processing, preparing, transporting, or holding food. Total DBP may not exceed 30 percent by weight of the rubber product (21 CFR 177.2600).[38] There is no concentration limit for the use of DMP in semirigid and rigid acrylic and modified acrylic plastics used as articles intended for use in contact with food (21 CFR 177.1010).[38] There is no limit in the amount of DEP that may be used in surface lubricants used in the manufacture of metallic articles that contact food (21 CFR 178.3910).[38] DEP may be used as a plasticizer in the manufacturer of food-packaging materials with no specific limits. This DEP will not be considered a "food additive" if of good commercial grade, suitable for association with food, and used in accordance with good manufacturing practice; the amount of DEP that migrates into food as a result of its use in food-packaging materials should not be intended to accomplish any physical or technical effect in the food itself and should be reduced to the least amount reasonably possible (21 CFR 181.22, 181.27).[38]

GENERAL BIOLOGY

Microbial Metabolism and Toxicity

A variety of bacteria can use DBP or DMP as a carbon source. The corresponding monoesters, phthalic acid, and protocatechuic acid are intermediates in the degradation of these chemicals.[40,41]

The growth of *Pseudomonas aeruginosa* was not inhibited by concentrations of up to 1000 ppm DMP. A 1500 ppm solution slightly inhibited the growth of the organism. After a 24-hour incubation, the concentration of a 98 ppm DMP solution decreased to 88 ppm, suggesting some bacterial utilization of the compound.[41] The concentration of neutralized DEP that inhibited the multiplication of *Pseudomonas putida* was greater than 400 ppm.[42] The minimum inhibitory concentration of a 10 percent solution of DEP in 95 percent ethanol was 1000 ppm for *Corynebacterium* sp. and greater than 1000 ppm for *Staphylococcus aureus* and *Escherichia coli*.[43]

The growth of the blue-green alga, *Microcystis aeruginosa*, was inhibited by 100 to 300 ppm of DMP and suppressed for 3 days by 400 ppm DMP. After 4 days, cellular lysis was observed in the 400 ppm DMP culture. Concentrations of DMP from 500 ppm to 800 ppm completely destroyed the cells within 72 hours.[44,45] Neutralized DEP inhibited the multiplication of *M. aeruginosa* at a concentration of 15 ppm and inhibited the multiplication of the green alga, *Scenedesmus quadricauda*, at a concentration of 10 ppm.[42,46]

A 10 ppm solution of DBP in phosphate buffer at pH 7 decreased the percent survival of the yeast, *Saccharomyces cerevisiae*, throughout a 48-hour incubation; a 20 ppm solution was even more toxic.[47] The minimum inhibitory concentration of a 10 percent (w/v) solution of DEP in 95 percent ethanol was 500 ppm for the fungus, *Candida albicans*.[43]

A concentration of 50 ppm of DBP completely inhibited the growth of cells of the protozoan, *Tetrahymena pyriformis*. Other phthalate esters were inhibitory as well.[48] A concentration of 1000 ppm of DMP markedly inhibited the growth rate of *T. pyriformis*.[44,49] Neutralized DEP inhibited the multiplication of the flagellate protozoan, *Entosiphon sulcatum* at a concentration of 19 ppm.[42]

In Vitro Cell Toxicity

The metabolism and toxicity of DBP, DMP, and DEP in cultures of mouse fibroblast and rat cerebellum and various human cell lines have been investigated.

Dose–response curves were produced, and the ID_{50} for the mouse fibroblast cultures, defined as the dose required to inhibit growth by 50 percent, was determined for the phthalates. The ID_{50}s for DBP, DMP, and DEP were 1×10^{-4}, 7×10^{-3}, and 3×10^{-3} mole/l, respectively. DMP was highly toxic to the cells when they were undergoing significant protein turnover.[13] The effect of DMP on a replicating mouse fibroblastic cell culture was investigated. A radioactively labeled amino acid mixture (^{14}C) was added to the cultures, and the radioactivity was followed over a 96-hour incubation. Cells were relatively insensitive to growth inhibition by DMP, as measured by uptake of radioactivity, for the first 24 hours. However, between 24 and 96 hours, the uptake of radioactivity decreased continuously.[50]

Toxicity to mouse fibroblasts was also investigated using the cell overlay method. Pads containing 0.05 ml of a 50 mg/ml emulsion of the phthalates were placed on the agar surface (2.5 mg phthalates/pad), and the cells were observed for 48 hours. DMP and DEP were toxic to the cells and DBP was not.[51] In another study, mouse fibroblastic cells were incubated for 24 hours with paper discs containing pure DMP and DEP or saline solutions saturated with DMP and DEP at pH 6. Only the pure DMP was toxic to the cells.[52] Other researchers have reported that all three phthalates were toxic in a 24-hour incubation of mouse fibroblastic cells.[53] The response of mouse fibroblastic cells to 1, 5, 10, and 50 percent suspensions of DBP, DMP, and DEP was studied by Oser et al.[54] All the suspensions were toxic except the 1 and 5 percent suspensions of DBP. In cell suspensions with DBP and DEP, the cellular ATP concentrations decreased over a 6-hour incubation.

The effects of DBP, DMP, and DEP on the outgrowth of nerve fibers and fibroblasts in primary cultures of rat cerebellum were investigated. The phthalates were added directly to the nutrient media. DBP and DEP completely inhibited

outgrowth at concentrations greater than or equal to 1.17×10^{-3} and 1.53×10^{-3} M, respectively. DMP did not completely inhibit outgrowth at concentrations less than or equal to 3.05×10^{-3} M.[55]

Human embryonic lung cell cultures were studied after the addition of 40 μg/ml of DBP to the culture medium. DBP inhibited cell growth and caused morphological changes in the cells, the appearance of lipid drops in the cytoplasm, and the accumulation of triacylglycerol in the cytosol.[56]

Thelestam et al.[57] found that DBP and DEP were inactive in a test in which the extent of membrane damage in human lung fibroblasts was determined by measuring the amount of a radioactively labeled cytoplasmic marker released into the media. The ID_{50} of DBP, defined as the concentration that caused 50 percent growth inhibition, for human diploid cell strain WI-85 was 1.35×10^{-4} M.[58]

Guess and Haberman[52] studied the effects of DBP, DMP, and DEP on human amnion and KB human cancer cells in culture. All three compounds killed and lysed the cells. Saline solutions saturated with DMP and DEP at pH 6 did not cause hemolysis of human erythrocytes.

HeLa cells were incubated for 7 days after the addition of DBP, DMP, and DEP to the culture medium. The 7-day IC_{50}s, the geometrical mean values between the totally inhibitory concentrations and the maximal completely noninjurious ones, were 3.1×10^{-2} M for DBP, 7.7×10^{-2} M for DMP, and 6.3×10^{-2} M for DEP.[59]

Effects on Enzymes

Phthalate esters have a variety of different effects on mammalian enzymes, both in vivo and in vitro. DBP and DMP affect drug-metabolizing enzymes in mammalian liver. Single-dose intraperitoneal administration of 3.05 ml/kg of DBP and 3.6 ml/kg of DMP to rats inhibited the activity of hepatic aminopyrine N-demethylase and aniline hydroxylase and had no effect on glucose-6-phosphatase, NADPH-cytochrome c reductase, and tyrosine aminotransferase activity. The activities of these enzymes were not decreased when the phthalates were administered intraperitoneally every day for 7 days.[60,61] Results of another study indicated that DBP weakly enhanced the activity of aminopyrine N-demethylase from rat hepatic 10,000 *g* supernatant.[62] The oral administration of 5 mmole/kg per day of DBP for 6 days to male rats increased the hepatic cytochrome P-450, had no effects on glutathione-S-transferase activity or the monooxygenase activities dependent on cytochrome P-450, increased the epoxide hydratase activity, and increased the conjugation of *o*-aminophenol and 4-methylumbelliferone with glucuronic acid. Rat liver incubated in vitro with 2×10^{-3} M DBP had no effect on epoxide hydratase or glutathione-S-transferase activities, decreased the monooxygenase activities, and decreased the conjugation of *o*-aminophenol and 4-methylumbelliferone with glucuronic acid.[63]

DBP, DMP, and DEP inhibited mitochondrial respiration. Concentrations of 5×10^{-5} to 1×10^{-3} M of the phthalates inhibited the respiration of isolated mitochondria from rat liver primarily by uncoupling oxidative phosphorylation rather than by inhibiting electron transport or energy transfer.[64,65] Other researchers using the same concentrations have suggested that the contrary is probably true; the phthalates inhibited electron transport or energy transfer.[66] In some studies,

DBP and DMP inhibited the activities of succinate dehydrogenase and ATPase, enzymes of the rat liver inner mitochondrial membrane, after intraperitoneal administration, and in in vitro assays at concentrations of 1×10^{-4} to 1.5×10^{-3} M.[62,65,67] DBP stimulated ATPase activity and induced swelling of rat liver mitochondria.[68]

Administration of 0.7 percent DBP or 0.5 percent DMP in the diet of male rats for 21 days increased hepatic weights and reduced serum cholesterol concentrations. Acetate incorporation into triglycerides and the steryl ester plus squalene and mevalonate incorporation into squalene plus sterols in liver minces were inhibited by dietary DBP. These results were not observed with DMP. DMP administration resulted in a decrease in total hepatic cholesterol and lipid. This was not observed with DBP.[69] The intraperitoneal administration of 20 mg/kg per day of DBP to mice for 16 days did not significantly lower serum cholesterol but did lower serum triglycerides. DBP, at a concentration of 2.5×10^{-6} M inhibited mouse liver homogenate acetyl-CoA synthetase, citrate lyase, and acetyl-CoA carboxylase but not fatty acid synthetase. These enzymes are involved in the cholesterol and triglyceride synthesis pathways.[70] A 5×10^{-6} M concentration of DBP and DEP inhibited in vitro human blood lecithin/cholesterol acyltransferase. DMP, at the same concentration, inhibited the enzyme slightly.[71]

DBP elevated the activities of mouse and rat serum lactate dehydrogenase, glutamic-oxalacetic transaminase, and glutamic-pyruvate transaminase.[72-74] DBP increased the activity of alkaline phosphatase in mice[72] but had no effect on this enzyme in rats.[73]

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

DMP was absorbed through human skin, and some of its metabolites were detected in human urine.[75]

A homogenate of rat epidermis metabolized DMP at approximately 1.5 percent of the rate of the metabolism of DMP by a homogenate of rat liver. The homogenates were compared on a mg wet weight basis. DMP was bound to the epidermis in quantities seven to eight times greater than those in which it was bound to an equal dry weight of hepatic tissue.[76]

DEP was absorbed through the skin of rabbits. Labeled DEP (^{14}C) was applied topically, and the application sites were covered with cotton patches. Analysis of urine indicated that approximately 9 percent of the radioactivity was excreted after 24 hours, 14 percent after 48 hours, and 16 to 20 percent within 72 hours. After 3 days of topical exposure, tissue distribution was determined by autoradiography. Radioactivity was detected in the lung, heart, liver, kidney, gonads, spleen, and brain. It was not detected in the skin and subdermal fatty tissue at the site of application.[13]

DBP was administered by gavage to male rats in two doses of 0.2 ml 24 hours apart. Urine was collected for 48 hours after the first dose, and DBP and its metabolites were quantitated. A total of 24.6 percent of the phthalate moiety was recovered in the urine. The recovered phthalate moiety consisted of 89.8 percent monobutyl phthalate (MBP), 2.7 percent phthalic acid (PA), 0.4 percent intact DBP, and four other metabolites in very small amounts. The researchers suggested that DBP was metabolized by hydrolysis of one ester bond and both terminal and subterminal oxidation of the remaining alkyl chain. The resulting primary

and secondary alcohols were, presumably, further oxidized to acids and ketones, respectively. DMP was administered by gavage to male rats in a single dose of 0.1 ml, and the urine was collected for 24 hours. A total of 44.6 percent of the phthalate moiety was recovered in the urine, and it consisted of 77.5 percent monomethyl phthalate, 14.4 percent PA, and 8.1 percent intact DMP. DMP appeared to be metabolized only by hydrolysis of one or both ester groups.[77]

Male mice were administered labeled DBP (^{14}C) orally or intravenously. The radioactivity accumulated in the liver and kidney within 6 hours of oral administration and within 1 hour of intravenous administration. The radioactivity was rapidly excreted in the urine and feces.[78]

DBP interacted with DNA in vitro, but after oral administration of labeled DBP (^{14}C) to mice, no radioactivity was recovered from hepatic DNA. DBP and its metabolites appeared not to be transported into the nuclei.[79]

Labeled DBP (^{14}C) was administered orally in dimethyl sulfoxide in a dose of 60 mg/kg or intravenously in saline in a dose of 10 mg/kg to male rats. Urine and feces were collected, and the amount of radioactivity excreted was determined. The percentage of administered radioactivity excreted varied from 81.4 to 97.7 in the urine and from 1.0 to 8.2 in the feces in the first 24 hours after oral or intravenous administration of DBP. Several rats were killed, and tissue distribution of radioactivity was determined. Brain, heart, liver, lung, spleen, muscle, adipose, stomach, prostate, and thymus tissues, blood, and the intestinal contents were examined 24 hours after oral or intravenous administration of DBP. Very little radioactivity was recovered. The elimination of DBP from tissues and organs was rapid, and no organ had any significant affinity for accumulation. Rats were administered labeled DBP (^{14}C) orally, and bile was collected. From 27.6 to 52.8 percent of radioactivity was excreted in the bile within 24 hours after oral administration of DBP. Since more radioactivity was excreted in the bile than in the feces, there was apparently good absorption of DBP and its metabolites from rat intestine. Urinary metabolites were identified in male rats, male hamsters, and male guinea pigs given a single oral dose of 60 mg/kg DBP. All 24-hour urine samples contained MBP as the major product, intact DBP, PA, MBP glucuronide, and two other MBP oxidation products. The hamster urine contained an additional oxidation product. The livers from rats were examined 1 hour after intravenous dosing of DBP, and the data obtained indicated that DBP was rapidly hydrolyzed to MBP by the microsomal fraction. No PA was detected. The bile contained MBP and intact DBP but not PA. Since PA was detected in the urine, it was suggested that its formation must occur at other sites than the liver. It was concluded that the hydrolysis of DBP to MBP occurred in the liver, that there was enterohepatic circulation of DBP and its metabolites and good absorption from the intestine, and that MBP was the main metabolite of DBP and was primarily excreted in urine.[62]

DBP and DMP, in concentrations of 0.4 mg/ml, were incubated at 37°C with rat liver and kidney homogenates. DBP and DMP almost completely disappeared after 2 hours of incubation with rat liver homogenates. The action of rat kidney homogenates was slower; however, approximately 90 percent of the DBP and 95 percent of the DMP disappeared during a 5-hour incubation. The phthalates were found not to be degraded spontaneously under these experimental conditions.[80]

A 500 mg/kg dose of labeled (^{14}C) DBP in ethanol was administered by gastric

intubation to male rats and the bile was collected every hour for 6 hours. Six hours after oral administration of DBP, 4.5 percent of the radioactivity was recovered in the bile. Five hours after intravenous injection of DBP, 10 percent of the radioactivity was detected in the bile. DBP bile metabolites included MBP, intact DBP, PA, an MBP glucuronide, and traces of other glucuronides. A small amount of DBP appears to be absorbed unaltered from the intestine, and the excretion of DBP through the biliary route has a role in its metabolic fate.[80]

Labeled DBP, DMP, and DEP (^{14}C) were incubated with rat, ferret, and baboon hepatic postmitochondrial supernatant and with intestinal-mucosal cell homogenates. All of the diesters were hydrolyzed by cell homogenates. They were all hydrolyzed by all the preparations, and greater than 90 percent of the total metabolite formed was the corresponding monoester. Baboon liver preparations hydrolyzed the diesters faster than rat liver preparations; ferret liver preparations were the least active. Baboon intestinal-mucosal cell preparations hydrolyzed the diesters faster than rat intestinal-mucosal cell preparations, and ferret intestinal-mucosal cell preparations were the least active.[81] Hepatic preparations from humans also catalyzed the monohydrolysis of DBP, DMP, and DEP. The toxic effects of phthalates administered orally may depend on the properties of the corresponding monoesters and/or alcohols.[82]

DBP, DMP, and DEP, in concentrations of 1 mg/ml, were incubated for 16 hours at 37°C with the contents of rat stomach, small intestines, or cecum or with suspensions of human feces. The phthalates were metabolized rapidly to the corresponding monoesters when incubated with the contents of rat small intestine. Metabolism was slower in the presence of rat cecal contents and only DMP was metabolized to any extent by rat stomach contents. Human feces were almost inactive in metabolizing the phthalates; DBP and DMP were metabolized faster than DEP. The intestinal contents of younger male rats metabolized DBP and DMP at a slower rate than intestinal contents from more mature male rats. Among adults, intestinal contents from male rats metabolized DBP at a faster rate than intestinal contents from female rats. The monoesters were the only products of metabolism; complete hydrolysis to PA did not occur. It may be significant toxicologically that there is a good correlation between rate of phthalate hydrolysis and the acute oral toxicity to rats that is reported in the literature. The more rapidly hydrolyzed phthalate esters are more toxic. In another experiment, rat intestinal contents were incubated at 37°C for 90 minutes or centrifuged or filtered before addition of DMP. Preincubation reduced the ability of the small intestine contents to degrade DMP. The enzymes involved in DMP metabolism appeared to be labile in vitro. Both centrifugation and filtration reduced the rate of DMP hydrolysis. The effect of antibiotics was studied by adding antibiotics to the incubation mixture or to the intestinal contents during the 90-minute preincubation period. The antibiotics used in the experiments were antibacterial enzymes. They had no effect on the rate of metabolism of DMP by small intestine contents, suggesting that the involved enzymes are not bacterial and more probably are mammalian in origin. Mucosal cell enzymes may be involved in DMP metabolism. The low rate of phthalate hydrolysis by rat cecal contents and human feces might be explained by the presence of a low number of active intestinal mucosal cells.[83] DBP was hydrolyzed by crude pancreatic lipase solution.[84]

The in vitro intestinal absorption of DBP and DMP was studied using an everted gut-sac preparation from the rat small intestine. In one experiment with

DBP, S,S,S,-tributylphosphorotrithioate (DEF), administered orally before gut-sac preparation, was used as an esterase inhibitor. Most of the DBP and DMP was hydrolyzed to the corresponding monoester before crossing the intestinal mucosa. Only 4.5 percent of the DBP and 18.8 percent of the DMP crossed the intestine intact. Inhibition of mucosal esterases by DEF reduced the amount of DBP hydrolyzed to MBP. Approximately the same amount of intact DBP was absorbed by the intestine with and without DEF, and DEF did not affect MBP absorption. Intestinal absorption of these compounds may be controlled by the hydrolysis of DBP to MBP.[85]

Labeled DEP (^{14}C) was administered intravenously to pregnant rats on Day 5 or Day 10 of gestation. Diester and/or metabolic products were present in maternal blood, fetal tissue, amniotic fluid, and placentas after Day 8 or Day 11, respectively, and throughout gestation.[86]

Phthalates are ubiquitous in the environment, and human exposure is likely. DBP was found in normal and diseased kidneys,[87,88] adipose tissue at autopsy,[89] in the blood of pregnant women, and in umbilical cords.[90] Possible routes of exposure to phthalates for humans are by oral or dermal contact, inhalation, or as a result of the use of medical devices, such as blood storage bags.[44]

ANIMAL TOXICOLOGY

Oral Studies

Acute Toxicity

The acute oral toxicity of DBP, DMP, and DEP was studied in rats,[84,91-97] mice,[72,91,98-100] rabbits,[91,101] guinea pigs, and chicks[91] (Table 3). The LD_{50} for rats administered DBP orally ranged from approximately 8 g/kg to 23.0 g/kg. The LD_{50} value for rats administered DMP orally was 6.9 ml/kg. In the Hodge and Sterner[102] classification of single-dose oral toxicity for rats, DBP and DMP would be classified as practically nontoxic to relatively harmless and as practically nontoxic, respectively.

The acute oral toxicity of two nail preparations, one containing 9 percent DBP and one containing 6 percent DBP, was studied in rats[104,105] (Table 3). Both preparations were practically nontoxic.

Subchronic and Chronic Toxicity

DBP, DMP, and DEP in corn oil were administered by oral intubation for 4 days to groups of 12 rats in doses of 7.2 mmole/kg per day (approximately 2.0 g/kg per day DBP, 1.4 g/kg per day DMP, and 1.6 g/kg per day DEP). There were no significant changes in food intake or body weight. DMP and DEP administration did not result in significant changes in testes weight, no testicular atrophy was observed, and urinary zinc excretion was unaffected. Administration of DBP decreased weight of testes and produced severe atrophy of the seminiferous tubules. Most of the tubules had complete loss of spermatocytes and spermatids. DBP administration was accompanied by an increase in the urinary excretion of zinc, and there was a decrease in the zinc content of testes on an absolute and relative weight basis.[106-108] The administration of zinc, concurrently with DBP, provided substantial protection against DBP-produced testicular damage.[106]

TABLE 3. Acute Oral Toxicity

Material Tested	*Method*	*Species of Animal*	*LD_{50}*	*Comments*	*Reference*
DBP	–	Rats	23.0 g/kg	–	92,97
DBP	–	Rats	12.5 g/kg	–	93,96
DBP	–	Rats Mice	14.95 g/kg 9 g/kg	–	103
DBP	–	Rats	>20 ml/kg	–	95
DBP	Animals were observed for 7 days following DBP administration	Male mice	9.77 g/kg	–	72,98
DBP	Oral administration of 200 mg DBP to 10 mice	Mice	–	6/10 of the mice died within 7 hours.	99
Undiluted DBP	Oral administration of 4, 8, 16, and 32 g/kg, of DBP to 3, 9, 6, and 6 rats, respectively	Rats	~8 g/kg	0/3, 4/9, 6/6, and 6/6 rats died, respectively. The 4 g/kg dose had no effect on growth, the 8 g/kg dose slightly inhibited growth, and the 16 and 32 g/kg dose groups succumbed too quickly to exhibit significant changes in growth	84
DBP	Animals were observed for 7 days following DBP administration	Male mice	Between 14.8 and 17.0 g/kg	–	98,100
Undiluted DMP	40 rats, 80 guinea pigs, and 120 chicks were fasted prior to DMP administration. 110 mice and 80 rabbits were not fasted. Animals were observed for 6 days following DMP administration. DMP was given to 10 animals/dose	Rats Mice Rabbits Guinea pigs Chicks	6.9 ml/kg 7.2 ml/kg 4.4 ml/kg 2.4 ml/kg 8.5 ml/kg	–	91
DEP	–	Rabbits	1.0 g/kg	–	101
DEP	–	Rats	8.2 ml/kg	–	94
Nail polish, 9 percent DBP	5 male and 5 female animals/dose were fasted 16 hours prior to oral intubation and were observed for 14 days after	Rats	>5 ml/kg	No signs of gross pathology on necropsy of rats receiving 5 ml/kg	104
Nail preparation, 6 percent DBP	Preparation administered by oral intubation to 10 animals	Rats	>5 g/kg	"Nontoxic"	105

DBP produced testicular atrophy in the rat, mouse, guinea pig, and ferret, but not in the hamster after oral administration in a dose of 2.0 g/kg per day for 10 days.[108]

Long-term oral toxicity of DBP, DMP, and DEP was studied in rats,[84,94-96,103,109-113] mice,[103] and rabbits[114] (Table 4). Except at dietary concentrations of 1.25 percent DBP for 1 year, 8.0 percent DMP for 2 years, and 5.0 percent DEP for 16 weeks,the phthalates were relatively nontoxic to rats in subchronic and chronic oral tests.

Dermal Studies

Acute Toxicity

The acute dermal toxicity of DMP to rabbits was determined by placing DMP in contact with the clipped skin and holding it in place with a rubber cuff. The rabbits were exposed for 24 hours and then observed for 2 weeks. The acute dermal LD_{50} of DMP to rabbits was greater than 10 ml/kg.[91]

Subchronic and Chronic Toxicity

DBP and DMP were tested for long-term dermal toxicity by applying 0.5, 1.0, 2.0, and 4.0 ml/kg per day for 90 days to the clipped, intact skin of rabbits. The chemicals were applied to approximately 10 percent of the body surface. The subchronic dermal LD_{50} of DBP to rabbits was greater than 4 ml/kg per day for 90 days. DBP was slightly irritating to skin and very irritating to rabbit penile mucosa. A slight dermatitis was observed, and in the 4 ml/kg dosed rabbits, slight renal damage (not further described) was observed.[95] The subchronic dermal LD_{50} of DMP to rabbits was also greater than 4 ml/kg per day for 90 days. No skin irritation or dermatitis was observed, although DMP was irritating to rabbit penile mucosa. Pulmonary edema and slight renal damage were observed in the rabbits that died during the study. Rabbit survivors had varying degrees of nephritis (not further described) at the two highest doses.[91]

Primary Irritation

DBP and DMP were applied to the clipped, intact, and abraded skin of 3 rabbits. The rabbits were exposed to 0.5 ml of the chemicals for 24 hours with an occluded patch. DBP caused "very slight irritation." DMP was not irritating except in molting areas and the Primary Irritation Index (PII) was 0.7.[91,95]

DMP was treated for primary irritation to rabbits using a pill box device. Pill boxes were affixed to shaved rabbit skin, and 0.1 ml of a 20 percent solution of formalin ("as the primary irritant") was painted onto the skin and allowed to dry. Discs containing 0.2 ml of DMP were placed in the pill box and the box was closed. A 0.25 ml volume of a 0.5 percent sterile Evans blue solution was injected intravenously. After 18 hours, the blue color at the pill box sites was evaluated and correlated with irritancy. Ten to 15 separate observations were made. DMP had an irritation score of 0.8 on a scale of 0 to 3; DMP was less than slightly irritating.[115]

Sensitization

No evidence of sensitization was observed in rabbits receiving daily topical applications of DBP and DMP at doses of up to 4.0 ml/kg per day for 90 days.[95]

Intradermal Irritation

The intradermal irritation of phthalates to rabbits was measured by injecting the phthalates into the skin of the shaven backs. A trypan blue solution was injected into the marginal ear vein, and the extravasated trypan blue at the injection site was used as a measure of the extent of the inflammatory response. In one study, 0.2 ml of 100 mg/ml phthalate emulsions was injected. DBP gave a mild inflammatory response after 10 minutes and a moderate response after 26 minutes. A rapid and marked inflammatory response to DMP and DEP was noted.[51] Other researchers used cottonseed oil as a diluent for DBP, DMP, and DEP. DBP was not irritating, but DMP and DEP produced a significant degree of irritation.[116] In another study, saline solutions saturated with the phthalates were administered. No response was observed to DMP and DEP.[52]

Eye Irritation

The eye irritation potential of DBP, DMP and DEP was studied in rabbits.[116-118] The eye irritation potential of nail preparations containing 9 percent DBP and 6 percent DBP also was investigated[105,119] (Table 5). DBP, DEP, and nail preparations containing DBP were relatively nonirritating to the rabbit eye. With long contact time, undiluted DMP may be injurious to the eyes of rabbits.

Inhalation Studies

Male rats were exposed to 1.5 mg/m^3 of DBP vapor for 6 hours per day and 6 days per week for approximately 1 month. There were no significant effects on body or organ weights when the rats were compared to controls. No significant toxic effects were observed.[73] Rats were exposed to 0.5 mg/m^3 and 50 mg/m^3 of DBP mist for 6 hours per day for 6 months. Rats exposed to either concentration had smaller weight gains and greater brain and lung weights than control rats. The higher concentration had a greater effect than the lower concentration.[120]

Intraperitoneal Studies

Acute Toxicity

Acute intraperitoneal toxicity of DBP, DMP, and DEP was studied in mice[51,52,116,121] and in rats[122] (Table 6). The acute intraperitoneal LD_{50}s for rats for DBP, DMP, and DEP were 3.05 ml/kg, 3.38 ml/kg, and 5.06 ml/kg, respectively.

Subchronic and Chronic Toxicity

DEP was administered intraperitoneally in a dose of 2 ml/kg per day to rabbits for 8 days. "Temporary distress" was observed during and after administration. There was no paralysis or other abnormal effect. The intraperitoneal administration of 1.5 ml/kg per day of DEP to guinea pigs for 8 days did not result in any permanent ill effects during or after the experiment.[114] A DEP emulsion was administered intraperitoneally in a dose of 125 mg/kg per day for 6 weeks to 20 to 30 mice. There was slight retardation in weight gain and some evidence of peritonitis. The organ:body weight ratios for liver, heart, lungs, kidneys, spleen, and testes of treated mice were not different from the control mice ratios. No abnormal hematological patterns were observed.[51]

TABLE 4. Subchronic and Chronic Oral Toxicity

Material Tested	*Dose and Vehicle*	*Length of Study*	*Number and Species of Animals*	*Results*	*Reference*
DBP	1 ml/kg in oil 2 times a week	6 weeks	Rats	No adverse effects were reported	109,113
DBP	20 mg/kg	11 weeks and 3 days	Rats Mice	Leukocytosis was observed in rats. Mouse growth was inhibited	103
DBP	0.12 and 1.2 g/kg per day suspensions in olive oil	3 months	10 male and 10 female rats/dose, 40 control rats given only olive oil	1/10 rat from the high dose group died. No specific cause of death was determined. Both DBP doses produced a statistically significant increase in the animals' mean liver weight. No histological evidence of any pathologic changes were found in the liver, kidneys, and spleen	96
DBP	2.5 mg/kg per day	6 months	Rats	No adverse effects were observed	94,112
DBP	0.125 percent in the feed	1 year	20 male and 20 female rats in dosed and in control groups	6/40 rats from the dosed group died. No specific cause of death was determined. No "remarkable" alterations were observed upon gross and histological examination of liver, kidneys, and spleen of dosed rats	96
DBP	0.01, 0.05, 0.25, and 1.25 percent in the feed	1 year	10 rats/dose, 10 control rats	At 0.25 percent in the diet or lower, there was no effect on growth or survival. At 1.25 percent in the diet, 5/10 rats died during the first week. The remaining rats gained weight as did the controls. No rats exhibited significant changes in the number or distribution of elements in the peripheral blood or specific gross pathological changes	84
DBP	1 ml/kg in oil 2 times a week	1½ years	Rats	No pathological changes observed. No effects on hematological parameters or on organ weights	109,111, 133

DMP	2.0, 4.0, and 8.0 percent in the feed	2 years	10 female rats/dose	2.0 percent in the feed had no effect on growth. 4.0 and 8.0 percent had a slight but significant effect on growth. Chronic nephritis seen in rats on 8.0 percent in diet. Mortality rates were not different from those for control rats	95
DEP	3 ml/kg per day	8 days	Rabbits	The rabbits appeared normal for the 8 days and for 2 weeks afterwards. "Temporary distress" was observed after DEP administration	114
DEP	0.2, 1.0, and 5.0 percent in the feed	2, 6, and 16 weeks	5 male and 5 female rats in dosed and control groups on diet for 2 and 6 weeks. 6 rats of each sex, litter mate-paired, in 5.0 percent diet and control groups for 16 weeks. 15 rats of each sex in dosed and control groups on diet for 16 weeks	No changes in behavioral patterns or clinical signs of toxicity were observed. Both sexes on 5.0 percent feed and females on 1.0 percent feed consumed less food and gained less weight than the controls. There was a pattern of reduction in absolute weight and an increase in relative weight of the brain, spleen, heart, kidneys, adrenal glands, gonads, and pituitary of rats on the 5.0 percent diet. A pattern of increases in absolute and relative weights was observed in livers and various parts of the GI tract in these rats. Both liver and kidneys were enlarged but histologically normal	110

TABLE 5. Rabbit Eye Irritation

Material Tested	*Method*	*Results*	*Reference*
DBP	Undiluted DBP instilled into eyes. Eyes examined at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 24.0, and 48.0 hours postinstillation	No grossly observable irritation at any examination time	116
DMP	0.5 ml undiluted DMP applied to corneal center while eyelids are retracted. Lids released after 1 minute. Eye injury scored on a scale of 0–20 points after 18–24 hours	Injury score was >0.1 and <5.0. 5.0 is the level representative of severe injury; necrosis visible after staining and covering ~75 percent of the surface of the eye	117
DMP	0.1 ml undiluted DMP instilled into the conjunctival sac of the eyes. Injury scored on a scale of 0–110 points after 1 and 24 hours	Score was 3.3 after 1 hour and 2.2 after 24 hours	118
DMP	Undiluted DMP instilled into eyes. Eyes examined at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 24.0, and 48.0 hours postinstillation	No grossly observable irritation at any examination time	116
DEP	0.1 ml undiluted DEP instilled into the conjunctival sac of the eyes. Injury scored on a scale of 0–110 points after 1 and 24 hours	Score was 3.2 after 1 hour and 1.5 after 24 hours	118
DEP	Undiluted DEP instilled into eyes. Eyes examined at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 24.0, and 48.0 hours postinstillation	No grossly observable irritation at any examination time	116
Nail polish, 9 percent DBP	0.1 ml instilled into the conjunctival sac of one eye of 9 rabbits. Lids held together for 1 second. In 3 rabbits, treated eye washed at 30 seconds with 20 ml water. Scored on a scale of 0–110 at 24, 48, and 72 hours and 4 and 7 days postinstillation	Unwashed eyes' average score were 11.3, 9.7, 6.8, 4.8, and 0.5 and washed eyes' average scores were 8.3, 7.7, 4.0, 2.7, and 0.3 at 24, 48, and 72 hours and 4 and 7 days postinstillation, respectively	119
Nail preparation, 6 percent DBP	0.1 ml instilled into conjunctival sac of one eye of 6 rabbits. Lids held together for 1 second. Ocular reactions recorded at 24, 48, and 72 hours	No positives for conjunctival redness or chemosis, keratitis, or iritis. "Nonirritating"	105

A series of doses of DBP, DMP, and DEP was injected intraperitoneally into groups of 10 male mice 5 days a week. The apparent LD_{50} was calculated each week until it remained constant for 3 weeks; this was the chronic LD_{50}. DBP, DMP, and DEP reached chronic LD_{50}s in 25, 18, and 14 weeks, respectively. The chronic LD_{50} values were 0.85 ml/kg per day 5 days a week for DBP, 1.18 ml/kg per day 5 days a week for DMP, and 1.39 ml/kg per day 5 days a week for DEP.[116]

Other Studies

The acute intravenous LD_{50} of DBP to male mice was 0.72 g/kg.[72,98] DEP, in a 3 percent acacia suspension, was administered to an anesthetized rabbit through the jugular vein. The DEP was administered in repeated doses of 50 mg/kg to a total dose of 650 mg/kg (time between doses was not given). The first six doses caused a transient fall in blood pressure. The total dose of 650 mg/kg did not cause death or significant change in the animal. Five doses of the 3 percent acacia vehicle did not produce any blood pressure changes.[51] A 0.25 ml/kg dose of DEP in saline was injected slowly into the femoral vein of a dog. At first, respiration was stimulated and then it was paralyzed. The intravenous administration of 0.5 ml of DEP into a rabbit ear vein caused convulsions "similar to those produced by strychnine" within a few minutes. The symptoms "soon" disappeared and the rabbit appeared normal. A larger dose was fatal to rabbits by causing paralysis of respiration.[114]

The intramuscular administration of DBP in a dose of 4 g/kg to 3 rats and 8 g/kg to 3 rats did not result in any deaths, and there was no effect on the growth of the rats.[84]

The subcutaneous LD_{50} of DEP to guinea pigs was greater than or equal to 3 g/kg.[44,101]

SPECIAL STUDIES

Animal Reproduction and Teratology

DBP in doses of 2 and 4 ml/kg, DMP in doses of 0.5, 1, and 2 ml/kg, and saline in a dose of 4 ml/kg were administered intraperitoneally on Days 3, 6, and 9 of gestation to groups of 5 pregnant female rats. Day 1 of gestation was the day sperm were found in vaginal smears. Five control rats survived, and four of those implanted. Five and four rats survived, and four and three implanted, respectively, in the 2 and 4 ml/kg DBP groups. DBP administration resulted in a 50 percent reduction in the number of pups weaned per litter. Two male pups, one from each of two litters in the 2 ml/kg DBP group, had no eyes. In the 0.5, 1, and 2 ml/kg DMP groups, 5, 2, and 5 rats survived, and 4, 1, and 5 implanted, respectively. The numbers of pups weaned were not significantly different from the controls.[123] In another study in which Day 1 of gestation was the day after sperm were found in vaginal smears, groups of 5 pregnant female rats were administered DBP, DMP, and DEP intraperitoneally, in doses of 1/3, 1/5, and 1/10 of a previously determined acute intraperitoneal LD_{50} (3.05 ml/kg for DBP, 3.4 ml/kg for DMP, and 5.06 ml/kg for DEP), on Days 5, 10, and 15 of gestation (Table 7). Control rats were untreated or were administered distilled water, normal saline, or cottonseed oil. The rats were killed on Day 20, 1 day before expected

TABLE 6. Acute Parenteral Toxicity

Material Tested	*Method*	*No. and Species of Animals*	*LD_{50}*	*Comments*	*Reference*
DBP	Single IP injection of 4 dose levels ranging from 0.5 to 16 g/kg	Mice	4.00 g/kg	–	51
DBP	Single IP injection. Pathological changes observed up to 72 hours. Deaths recorded for 7 days	Female mice	14.9 mmole/kg	Pulmonary congestion, edema, and petechial hemorrhage, toxic reaction in spleen, and renal tubular degeneration observed after 72 hours	121
DBP	Undiluted DBP administered and animals observed 7 days for deaths; 2 ml/kg administered IP, 2 mice sacrificed at Days 1, 2, 4, 7, and 10, and heart, lung, kidneys, spleen, liver, pancreas, and bowel examined histologically for irritation	10 male mice/dose to determine LD_{50}; 10 mice of unspecified sex for histology	3.57 g/kg (3.41 ml/kg)	No evidence of significant intraperitoneal irritation	116
DBP	Animals observed for 7 days after IP injection	Female rats	3.05 ml/kg	–	122
DMP	Single IP injection of 4 doses ranging from 0.5 to 16 g/kg	Mice	1.58 g/kg	–	51
DMP	Single IP injection of saline saturated with DMP. 25 ml/kg DMP	Mice	–	No deaths observed	52
DMP	Single IP injection. Pathological changes observed up to 72 hours. Deaths recorded for 7 days	Female mice	18.8 mmole/kg	Pulmonary congestion and atelectasis, toxic reaction in spleen and lymph nodes, and renal tubular necrosis observed after 72 hours	121
DMP	Undiluted DMP administered and animals observed 7 days for deaths; 2 ml/kg administered IP, 2 mice sacrificed at Days 1, 2, 4, 7, and 10, and heart, lungs, kidneys, spleen, liver, pancreas, and bowel examined histologically for irritation	10 male mice/dose to determine LD_{50}; 10 mice of unspecified sex for histology	3.98 g/kg (3.35 ml/kg)	No evidence of significant intraperitoneal irritation	116
DMP	Animals observed for 7 days after IP injection	Female rats	3.38 ml/kg	–	122

DEP	Single IP injection of 4 doses ranging from 0.5 to 16 g/kg	Mice	2.83 g/kg	–	51
DEP	Single IP injection of saline saturated with DEP. 25 ml/kg DEP	Mice	–	No deaths observed	52
DEP	Single IP injection. Pathological changes observed up to 72 hours. Deaths recorded for 4 days	Female mice	12.4 mmole/kg	Pulmonary congestion, edema and petechial hemorrhage, toxic reaction in spleen, and renal tubular degeneration observed after 72 hours	121
DEP	Undiluted DEP administered and animals observed 7 days for deaths; 2 ml/kg administered IP, 2 mice sacrificed at Days 1, 2, 4, 7, and 10, and heart, lungs, kidneys, spleen, liver, pancreas, and bowel examined histologically for irritation	10 male mice/dose to determine LD_{50}; 10 mice of unspecified sex for histology	3.22 g/kg (2.87 ml/kg)	No evidence of significant intraperitoneal irritation	116
DEP	Animals observed for 7 days after IP injection	Female rats	5.06 ml/kg	–	122

TABLE 7. Embryotoxic and Teratogenic Effects of Phthalates[122]

Treatment Groups	*Volume Injected* (ml/kg)*	*Number of Corpora Lutea*	*Number of Resorptions†*	*Number of Dead Fetuses†*	*Number of Live Fetuses†*	*Number of Gross Abnormalities‡*	*Number of Skeletal Abnormalities***
Untreated controls	None	60	0	0	59 (100)	0	0
Distilled water	10.00	59	4 (6.8)	0	55 (93.2)	0	0
Normal saline	10.00	62	7 (11.5)	0	54 (88.5)	1 (1.9)	4 (14.3)
Cottonseed oil	10.00	59	4 (6.8)	0	55 (93.2)	1 (1.8)	3 (10.7)
	5.00	54	3 (6.4)	0	44 (93.6)	0	0
DBP	1.017	64	23 (36.5)	0	40 (63.5)	0	8 (33.3)
	0.610	56	2 (3.6)	0	53 (96.4)	0	7 (24.1)
	0.305	56	4 (7.3)	0	51 (92.7)	0	6 (20.7)
DMP	1.125	55	17 (32.1)	5 (9.4)	31 (58.5)	4 (11.1)	9 (75.0)
	0.675	55	0	1 (1.9)	52 (98.1)	4 (7.5)	6 (35.3)
	0.338	65	21 (33.3)	0	42 (66.7)	4 (9.5)	4 (25.0)
DEP	1.686	57	2 (3.6)	0	54 (96.4)	0	13 (81.3)
	1.012	59	0	0	57 (100.0)	0	8 (47.1)
	0.506	65	28 (44.4)	0	35 (55.6)	0	5 (26.3)

*5 pregnant female rats injected IP on Days 5, 10, and 15 of gestation and sacrificed on Day 20.

†Numbers in parentheses are percent values based on total number of implantations.

‡Numbers in parentheses are percent values based on total number of viable and nonviable fetuses.

**Numbers in parentheses are percent values based on total number of stained fetuses. Generally 30–50 percent of the fetuses were stained.

parturition. Phthalate administration did not interfere with fertility, as reflected by corpora lutea:implantation site ratio. However, there were significant effects upon embryonic and/or fetal development. The average weights of the fetuses from the treated groups and those administered saline were significantly lower than the average weight of the fetuses from the untreated controls. The investigator normally selected 30 to 50 percent of the fetuses for visualization of skeletal abnormalities. There was a significantly higher number of skeletal abnormalities in the fetuses from the test group as compared to the controls.[122] The failure to include historical control data, as well as a positive control in the test program, makes it difficult to evaluate the significance of the results.

DBP was administered in the feed to pregnant mice throughout gestation, and the mice were killed on Day 18. Day 0 of gestation was the day on which a vaginal plug was found. DBP was administered in five dietary concentrations from 80 to 2100 mg/kg. Implantation was not affected, but resorptions and fetal deaths increased with dosage. Maternal weight gain was depressed at the higher dosages and was due to increased embryonic or fetal death. Two of three live fetuses from the 2100 mg/kg DBP group had neural tube defects. Ossification was depressed, but malformation and resorption rates and fetal weights were not significantly affected by DBP administration up to 350 mg/kg per day.[124] In another study, 120 and 600 mg/day of DBP in olive oil were administered by gavage to groups of 10 female rats for approximately 3 months prior to their being mated. Additional groups of female rats received the same doses for 21 days following fertilization. The uteri and fetuses from all the rats were removed on Day 21 of gestation. Fetuses from treated and control rats did not differ significantly in number of sternum ossification foci, in development of the bones of the base of the skull or in the paws of the front and hind extremities, and in rib fusion. The administration of DBP before gestation did not cause any significant changes in other measured parameters. Administration of DBP to pregnant rats did result in lower placental weights, and fetal weights were significantly lower in the high DBP dose group. There were 4, 2, and 22 resorptions in the control, 120, and 600 mg/day DBP groups, respectively.[96]

The dietary administration of DBP, in doses of 10 and 100 mg/kg per day, to two mouse strains for three generations increased the formation of renal cysts in the F_1 and F_2 generations.[98,125] In another three-generation reproduction study, female rats were dosed daily for 6 weeks with 50 percent DBP solution in oil, at a dose of 1 ml/kg, and then were paired with untreated males. The offspring were bred to produce two additional generations; it is not known whether the second and third generations were dosed with DBP. No impairment of reproductive performance was noted. Development, growth, and fertility were normal for all three generations.[109,111,113]

Mutagenesis

The mutagenic activity of DBP, DMP, and DEP for *Salmonella typhimurium* mutants depended on the assay protocol. In the standard Ames test,[126] DBP and DEP were negative in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 with and without metabolic activation.[98,127,128] DEP was also negative in these strains when using a preincubation protocol.[129] In a liquid suspension assay with a 4-hour incubation, DBP, DMP, and DEP were positive in strain TA100

without metabolic activation and negative with metabolic activation.[130] In a modified Ames test in which histidine and biotin were incorporated into the bottom agar, DBP, DMP, and DEP were negative with and without metabolic activation in strain TA98, and DBP was negative with and without metabolic activation in strain TA100. DMP and DEP were positive in strain TA100 without metabolic activation, and the response was dose related. They were negative in strain TA100 with metabolic activation.[76,131] DBP and DEP were not mutagenic to *E. coli*.[98,132]

DNA repair enzyme-deficient *Bacillus subtilis* and *E. coli* were equally or less sensitive to DBP and DEP than the wild-type bacteria.[98,128] Rosenkranz and Leifer[133] reported that DBP did not affect either the wild-type or the DNA repair enzyme-deficient *E. coli*. There were no measurable zones of growth inhibition for either strain.

DBP was tested for mutagenic activity by reversion analysis of the yeast, *S. cerevisiae*. DBP had no mutagenic effect on the yeast whether the test was conducted with or without metabolic activation.[47]

The effects of DBP on Chinese hamster cell chromosome aberrations and sister chromatid exchanges (SCEs) have been investigated in several studies. In one study DBP was negative for chromosome aberrations and SCEs.[128] In another study, the mitotic index was not appreciably decreased when the cells were exposed to DBP in ethanol. A significant increase over the vehicle for the number of SCEs was found, but no dosage effect was found for chromosome aberrations or SCEs.[134] DBP in a 0.2 percent bovine albumin solution was examined in a third study. The percentages of chromosome aberrations with DBP and with bovine albumin were 6 and 1.8 percent, respectively. These results did not conclusively prove that DBP caused chromosome aberrations; DBP was called a suspicious compound by the researchers.[135] DBP, DMP, and DEP, in doses of 0.25 mg/ml, had no effect on chromatid aberrations in human leukocyte cultures compared to controls.[136]

Carcinogenesis

DBP was noncarcinogenic, but specific details of experiments are lacking.[128,134] Carcinogenesis has not been observed in 18-month or longer DBP feeding studies in rats.[137]

Di(2-ethylhexyl)phthalate (DEHP), a compound currently of great concern, is not used in cosmetics. DEHP was tested in a National Toxicology Program carcinogenesis bioassay and was carcinogenic in both rats and mice.[138]

CLINICAL ASSESSMENT OF SAFETY

Dermal Studies

Patch tests have been performed on human subjects with the phthalates.[139,140] The cosmetic industry has conducted studies on the skin irritation, sensitization, and photosensitization of a variety of products containing DBP[141-148] (Table 8). DBP, DMP, and DEP in concentrations of 2 percent in petrolatum and DBP at 5 percent in petrolatum were nonirritating in 48-hour closed patch tests; the 2 percent concentrations were tested on 1532 subjects with 1

positive reaction, and the 5 percent DBP was tested on 53 subjects with no positive reactions. Products containing DBP in concentrations ranging from 4.5 to 9 percent were tested at a concentration of 100 percent. A nail polish containing 9 percent DBP was slightly irritating in a 23-hour patch test on 13 subjects and not irritating in a 48-hour patch test on 25 subjects. The nail polish was tested in a modification of the maximization test on 25 subjects, and no contact sensitization was observed. A deodorant containing 4.5 percent DBP was tested in an antiperspirant efficacy test on 43 subjects; the deodorant was not irritating. It was slightly irritating in a 21-day cumulative irritancy test on 12 subjects. The deodorant was not an allergen in a modification of the repeated insult patch test on 200 subjects. A nail preparation containing 6 percent DBP was tested on 99 subjects in a prophetic patch test, on 48 subjects in a repeated insult patch test, and on 47 subjects in a controlled use study; the nail preparation was nonirritating and nonsensitizing. The nail preparation was also tested for photosensitization in the prophetic patch test and the repeated insult patch test; it was nonphotosensitizing.

Other Studies

A chemical worker accidentally swallowed approximately 10 g of DBP. The worker's symptoms included nausea, vomiting, dizziness, headache, pain and irritation in the eyes, conjunctivitis, and toxic nephritis. He recovered completely after 2 weeks.[94,149]

Proper treatment of a human corneal burn caused by DMP resulted in healing within 48 hours and no loss of vision.[150]

The health status of 147 workers subjected to prolonged occupational exposure to mixtures of phthalate plasticizers (including DBP) was investigated; many workers had a moderately pronounced toxic polyneuritis.[151]

SUMMARY

DBP, DMP, and DEP are dialkyl phthalates. They are primarily used in cosmetics at concentrations of less than 10 percent as plasticizers, solvents, and perfume fixatives.

Some bacteria can use DBP and DMP as carbon sources. These two phthalates and DEP may inhibit the growth of or be toxic to bacteria, algae, yeast, and protozoa. The phthalates may also inhibit the growth of or be toxic to mouse fibroblast, rat cerebellum, and various human cell lines. The phthalate esters have a variety of different effects on mammalian enzymes, both in vivo and in vitro.

Radioactive DBP, after oral administration to rats, hamsters, and guinea pigs, is rapidly metabolized to monobutyl phthalate and other products, and these metabolites are excreted in the urine and feces. In rats, the biliary route seems to be important in the metabolic fate of DBP. Only small amounts of radioactivity are found in rat tissues and organs after oral administration of labeled DBP (^{14}C). DMP is absorbed through human skin. Labeled DEP (^{14}C) was absorbed through the skin of rabbits, and the radioactivity was distributed throughout the body and excreted in the urine. Within several days of the intravenous administration of DEP to pregnant rats, DEP and its metabolic products were found in maternal blood, fetal tissue, amniotic fluid, and placentas.

TABLE 8. Skin Irritation and Sensitization

Material Tested	*Concentration (percent)*	*Method*	*Number of Subjects*	*Results*	*Reference*
DBP	5 percent in petrolatum	48-hour closed patch test on back. Readings 48 and 72 hours after patch application	7 men and 46 women who wore dentures and suffered from "burning mouth syndrome"	No positive reactions	139
DBP, DMP, and DEP	All phthalates at 2 percent in petrolatum	48-hour closed patch test. Joint study by International Contact Dermatitis Research Group	1532	1 positive reaction	140
Nail polish, 9 percent DBP	100	21 23-hour patches on same site on back. 1 hour rest. Scored (0–3) 1 hour after patch removal	2 men and 11 women	Composite total score was 247 (out of a possible maximum of 819). "Slightly irritating"	147
Nail polish, 9 percent DBP	100	48-hour occluded patch to back or forearm	25	No irritation observed	148
Nail polish, 9 percent DBP	100	Modification of the maximization test.[152] 5 48-hour occluded induction patches on back or forearm with 24-hour rests in between them; 24-hour sodium lauryl sulfate (SLS) pretreatment before first patch. 10-day rest period. 1-hour SLS pretreatment followed by 48-hour challenge patch; scored at patch removal and 24 hours later	25	"No instances of contact sensitization"	148
Deodorant, 4.5 percent DBP	100	Antiperspirant efficacy test, normal use conditions (Federal Register 43:46694-732, October 10, 1978). Applied 0.5 g/day for 2 days	43	"No irritation observed" in the axillary region	146
Deodorant, 4.5 percent DBP	100	Modification of the repeated insult patch test.[153,154] 8 48-hour induction patches of 0.2 g on upper arms. 2-week rest 72-hour challenge at original and new sites. Scored at 48 and 96 hours (0–3)	41	9 reactions of 1 (mild erythema) at induction and 1 equivocal reaction at original site at 96-hour challenge observation. "Not an allergen under conditions of the test"	144

Deodorant, 4.5 percent DBP	100	21-day cumulative irritancy test.[155] 21 24-hour occluded patches of 0.3 g applied to the back over 21 days. Each patch scored at removal (0–4)	1 man and 11 women	Total score calculated on the basis of 10 subjects was 140.8 out of a possible maximum of 840. "Slightly irritating"	143
Deodorant, 4.5 percent DBP	100	Modification of the repeated insult patch test.[153,154] 10 24–48 hour occlusive induction patches of 0.2 g ~ 3 times a week. Patches applied to the back. 10-day rest. 72-hour challenge patch. Scored after patch removal (0–4)	159	4 equivocal reactions and 1 score of 1 (erythema) during induction. One equivocal and 1 score of 1 at challenge. "Does not appear to be an allergen under test conditions"	145
Nail preparation, 6 percent DBP	100	Prophetic patch test.[156] 2 24-hour open and closed patches 10 to 14 days apart. 1 open patch irradiated for 1 minute at a distance of 12 in with a Hanovia Tanette Mark I lamp (UV). Scored at patch removal and daily for 5 days thereafter (1+ to 3+)	99	No positive reactions were observed. "Nonirritating, nonsensitizing, nonphotosensitizing"	141
Nail preparation, 6 percent, DBP	100	Repeated insult patch test.[157] 10 24-hour open and closed induction patches 24 hours apart. 2–3 week rest. 48-hour challenge patches. Open and closed patches at inductions 1,4,7, and 10 and at the challenge were irradiated for 1 minute at a distance of 12 in with a Hanovia Tanette Mark I lamp (UV). Scored at patch removal (1+ to 3+)	48	Five 1+ and one 2+ reactions to open patches at induction. One reaction to an open patch at UV challenge. "Nonirritating, nonsensitizing, nonphotosensitizing"	141
Nail preparation, 6 percent DBP	100	Controlled use study for 4 weeks. Fingernails and eyes were examined each week (1+ to 3+)	47	No positive reactions were observed. "Nonirritating"	142

DBP and DMP are degraded by renal homogenates from rats. Both of these phthalates and DEP are hydrolyzed by rat, ferret, and baboon liver and intestinal-mucosal cell homogenates. The phthalates are also metabolized by human liver homogenates and rat intestinal contents. The enzymes involved in DMP metabolism by rat intestinal contents are labile in vitro and mammalian in origin. DMP is hydrolyzed by the gastric contents of rats. Human feces are relatively inactive in degrading the phthalates.

Phthalates are ubiquitous in the environment, and human exposure is likely. DBP has been found in the kidneys, adipose tissue, blood, and umbilical cords of humans.

The acute oral LD_{50} value of DBP for rats ranged from approximately 8 g/kg to 23.0 g/kg; DBP was practically nontoxic to relatively harmless. DMP was practically nontoxic; it had an acute oral LD_{50} value for rats of 6.9 ml/kg. The LD_{50} for rabbits for DEP administered orally was 1.0 g/kg. No adverse effects were reported after the oral administration of doses of DBP of 2.5 mg/kg per day for 6 months or 1 mg/kg two times a week for 1½ years to rats, or of a DBP concentration of 0.25 percent in the feed of rats for 1 year. At doses of 20 mg/kg of DBP for 80 days, growth was inhibited in mice and leukocytosis was observed in rats. At a concentration of 1.25 percent DBP in the diet, 5 of 10 rats died within a week, but the remaining rats survived the diet for a year and appeared normal. A 2.0 percent dietary concentration of DMP fed for 2 years to rats had no effect on growth, 4.0 and 8.0 percent inhibited growth, and rats fed 8.0 percent had chronic nephritis. Doses of DEP of 3 ml/kg per day for 8 days and a 0.2 percent concentration of DEP in the diet for up to 16 weeks had no adverse health effects in rabbits and rats, respectively. Concentrations of 1.0 and 5.0 percent DEP in the diet for up to 16 weeks reduced the growth of rats.

The oral administration of DBP produced testicular atrophy in the rat, mouse, guinea pig, and ferret but not in the hamster in a dose of 2.0 g/kg per day for 10 days. The simultaneous administration of zinc provided substantial protection against testicular damage in the rat. Testicular atrophy was not observed after the administration of DMP and DEP in oral doses of 7.2 mmole/kg per day (approximately 1.4 g/kg per day DMP and 1.6 g/kg per day DEP) to rats.

The acute dermal LD_{50} for DMP for rabbits was greater than 10 ml/kg. The subacute (90-day) dermal LD_{50}s of DBP and DMP to rabbits were greater than 4 ml/kg per day. At doses of 0.5 to 4.0 ml/kg per day, DBP was slightly irritating to skin, DMP was irritating in molting areas only, and there was no evidence of sensitization by either of the phthalates. Renal damage was observed in rabbits that died during this study, and survivors receiving 2.0 to 4.0 ml/kg per day of DBP and DMP had varying degrees of nephritis. Phthalate emulsions were injected intradermally into rabbits; DBP produced a mild to moderate inflammatory response, and DMP and DEP produced a marked inflammatory response. The results of other such experiments varied with the vehicle used.

Undiluted DBP, DMP, and DEP were instilled into the eyes of rabbits; irritation was minimal. However, with long contact time, DMP may be irritating to the rabbit eye.

The inhalation and intraperitoneal, intravenous, intramuscular, and subcutaneous administration of the phthalates have been studied in a variety of laboratory animals. Results depended on the route, the species, and the dose.

Several studies suggest that the administration of DBP, DMP, and DEP to

pregnant rats may increase the number of resorptions and have significant effects upon embryonic and fetal development. Gross and skeletal abnormalities in offspring have been observed in some cases. The dietary administration to three generations of mice of doses up to 100 mg/kg per day DBP has increased the formation of renal cysts in the second and third generations.

The mutagenic activity of DBP, DMP, and DEP toward *S. typhimurium* mutants depends on the assay protocol; studies have been both negative and positive in the same strains. DBP and DEP were not mutagenic for *E. coli*. DNA repair enzyme-deficient *B. subtilis* and *E. coli* were not more sensitive to DBP and DEP than the wild-type bacteria; one study reported that DBP did not affect either the DNA repair enzyme-deficient *E. coli* or the wild-type. DBP was negative in a *S. cerevisiae* reversion analysis with and without metabolic activation. DBP was both negative and positive for chromosome aberrations and sister chromatid exchanges in Chinese hamster cells; it has been called a "suspicious compound." DBP, DMP, and DEP have no effect on chromosome aberrations in human leukocyte cultures.

DBP was not carcinogenic in chronic (18-month or longer) feeding studies in rats.

There were no positive reactions among 53 human subjects patch tested with 5 percent DBP. One positive reaction was observed when 1532 subjects were patch tested with DBP, DMP, and DEP at a 2 percent concentration. Cosmetic formulations containing up to 9 percent DBP were tested in a variety of patch test procedures; in some procedures some of the formulations were slightly irritating. In other cases, no irritation was observed. Sensitization and photosensitization were not observed.

DISCUSSION

A comparison of the chemical structures of the phthalates suggests that DBP may have the greatest toxicological significance. Data are limited for both DMP and DEP, and, in particular, there are clinical phototoxicity and photosensitivity data only for a preparation containing DBP. However, the Panel believes that the information contained in this report is adequate for a safety assessment of all three phthalates.

DBP but not DMP and DEP caused testicular injury in laboratory animals. The combined teratogenic test data available to the Expert Panel are not adequate to conclude that DBP, DMP, or DEP are proven teratogens. The concentrations used in cosmetic products and the rapid metabolism and elimination of these ingredients, as indicated by experimental studies, minimize the significance of the observations of testicular damage by DBP and the conflicting teratogenic test results. The Panel notes that the information provided in the literature on the carcinogenicity of DBP is limited and does not permit an evaluation of the assays performed and the results obtained. The results of mutagenesis studies, however, are essentially negative.

CONCLUSION

On the basis of the available data, the Panel concludes that Dibutyl Phthalate, Dimethyl Phthalate, and Diethyl Phthalate are safe for topical application in the present practices of use and concentration in cosmetics.

ACKNOWLEDGMENT

Karen Brandt, Scientific Analyst and Writer, prepared the literature review and technical analysis used by the Expert Panel in developing this report.

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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 Table 8 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. Table 8 provides 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 gastrointestinal (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 NTP study, DBP, DEP, and DMP were not found to be dermal irritants or sensitizers, confirming previous data using human and animal subjects.

Although 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 in a 0.5% DBP feed group, or at 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.

TABLE 8
Historical and current cosmetic product uses and concentrations for Dibutyl, Diethyl, and Dimethyl Phthalate

Product category	1981 use (Elder 1985)	2001 use (FDA 2001)	1981 concentrations (FDA 1981) (%)	2001 concentrations (CTFA 2001a, 2001b, 2001c) (%)
		Dibutyl Phthalate		
Perfumes	—	—	—	38–890 ppm**
Hair sprays	—	—	—	55–160 ppm**
Shampoos (noncoloring)	—	—	—	0.007
Hair preparations (other noncoloring)	3	—	>0.1–1	—
Hair-coloring preparations (other)	3	—	>0.1–1	0.1
Aftershave lotions	3	—	>0.1–1	—
Hair bleaches	—	—	—	0.1
Makeup (other)	1	—	>0.1–1	0.5
Nail basecoats and undercoats	36	32	>1–10	1–6; 15*
Nail creams and lotions	—	2	—	5
Nail extenders	—	—	—	1; 1*
Nail polish and enamel	522	88	≤25	0.5–15; 15*
Nail polish and enamel removers	3	—	0.1–25	2
Nail care preparations (other)	14	25	≤25	5–7; 6*
Underarm deodorants	—	—	—	140–200 ppm**
Personal cleanliness products (other)	5	3	>1–5	—
Total uses/ranges for Dibutyl Phthalate	**590**	**150**	**0.1–25**	**0.0038–15**
		Diethyl Phthalate		
Baby shampoos	—	—	—	0.03
Baby lotions, oils, powders, and creams	—	—	—	0.00003
Baby products (other)	—	—	—	0.05
Bath oils, tablets, and salts	3	1	≤5	—
Bubble baths	—	—	—	0.06
Bath preparations (other)	2	2	≤0.1	0.008–0.09
Colognes and toilet waters	19	24	≤5	0.2–2
Perfumes	23	7	≤50	1–11
Powders	1	5	>0.1–1	—
Sachets	3	2	>0.01–5	—
Other fragrance preparations	2	11	>0.1–50	0.01–1 67–28,000 ppm**
Hair conditioners	—	—	—	0.1–0.2
Hair sprays (aerosol fixatives)	5	—	>0.1–5	0.4 17–1500 ppm**
Shampoos (noncoloring)	—	—	—	0.0008–0.2
Hair tonics, dressings, etc.	—	1	—	14–220 ppm**
Wave sets	1	—	>0.1–1	—
Face powders	—	—	—	0.4
Eye shadow	1	—	≤0.1	—
Eyebrow pencil	—	—	—	0.007
Mascara	—	—	—	0.007–0.07
Eye makeup preparations (other)	—	—	—	0.07
Foundations	—	—	—	0.3
Makeup (other)	—	—	—	0.0003
Nail polish and enamel	—	—	—	0.1
Nail polish and enamel remover	1	—	>1–5	—

(Continued on next page)

TABLE 8
Historical and current cosmetic product uses and concentrations for Dibutyl, Diethyl, and Dimethyl Phthalate *(Continued)*

Product category	1981 use (Elder 1985)	2001 use (FDA 2001)	1981 concentrations (FDA 1981) (%)	2001 concentrations (CTFA 2001a, 2001b, 2001c) (%)
Nail care preparations (other)	—	—	—	0.2
Bath soaps and detergents	1	—	>0.1–1	2
Underarm deodorants	—	4	—	0.3–1 20–3300 ppm**
Feminine hygiene deodorants	—	—	—	0.4
Other personal cleanliness products	—	—	—	1
Aftershave lotion	3	4	>0.1–1	0.5–2
Shaving cream (aerosol, brushless, and lather)	—	—	—	0.001
Other shaving preparation products	—	—	—	1
Skin-cleansing creams, lotions, liquids and pads	—	—	—	0.0002
Face and neck skin care preparations	1***	—	≤0.1***	0.3
Body and hand skin care preparations		2		0.008–0.5 26–190 ppm**
Foot powders and sprays	—	—	—	1
Night skin care preparations	—	—	—	0.0004
Paste masks (mud packs)	—	1	—	0.1
Skin fresheners	—	4	—	0.1–0.9
Skin care preparations (other)	1	5	>0.1–1	0.00003–0.9
Total uses/ranges for Diethyl Phthalate	**67**	**73**	**≤ 0.1–50**	**0.00003–2**
	Dimethyl Phthalate			
Hair conditioners	2	—	>0.1–1	—
Hair sprays (aerosol fixatives)	—	8	—	0.00002–2
Hair rinses	1	—	>0.1–1	—
Shampoos (noncoloring)	—	—	—	0.00002
Hair tonics, dressings, etc.	2	—	>0.1–5	—
Wave sets	2	—	>0.1–1	—
Hair preparations (other noncoloring)	4	3	>0.1–1	—
Hair color sprays (aerosol)	—	1	—	—
Blushers	—	—	—	0.00008
Face powders	—	—	—	0.00008
Foundations	—	—	—	0.005
Bath soaps and detergents	—	—	—	0.004
Underarm deodorants	—	—	—	33 ppm**–0.2
Aftershave lotions	—	—	—	0.2
Total use/ranges for Dimethyl Phthalate	**11**	**12**	**>0.1–5**	**.00002–2**

*Maximum concentrations reported by Nail Manufacturers Council (NMC 2001).

**Concentrations found in off-the-shelf products (Houlihan et al. 2002).

***These categories were combined when the original safety assessment was performed and are now separate categories.

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 the estrogen receptor and do not affect estrogen-regulated developmental endpoints. An antiandrogenic 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 sof phthalates have been detected in the urine of an adult reference population and in the urine of young children in a small pilot study.

The Centers for Disease Control and Prevention (2003) found that the urinary concentrations of the monoester metabolites of DBP and DEP in 2536 Americans were similar or slightly lower than those reported in a preliminary study of 289 adults (Blount et al. 2000). 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 RfDs. 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 (NTP 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 2000; 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 antiandrogenic 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 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, 2001b, 2001c; 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, 2001b, 2001c; Houlihan et al. 2002)
- 8.5% penetration through nail in 14 days (Jackson Research Association 2002)

280 mg/day $\times$ 15% $\times$ 8.5%/14 days = 0.255 mg/day/60 kg = 4.25 μg/kg/day and 4.25 μg/kg/day $\times$ 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
- 5% skin absorption (Mint et al. 1994)

5 g/day $\times$ 160 μg/g $\times$ 20% $\times$ 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 $\times$ 200 μg/g $\times$ 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 $\times$ 890 μg/g $\times$ 5% = 24 μg/day/60 kg = 0.4 μg/kg/day.

Total Exposure

- Sum of each of the separate exposures

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 was 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 of 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 5476. The Panel also noted that both NOAEL figures were obtained from rat studies, and detoxification 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 to 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.

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~~DIMETHICONE COPOLYOL~~

~~A safety assessment of Dimethicone Copolyol was published in 1982 with the conclusion that this ingredient "is safe as a cosmetic ingredient in the present practices of use and concentration" (Elder 1982). New studies, along with updated information regarding types and concentrations of use, were considered by the CIR Expert Panel. The Panel determined to not reopen this safety assessment.~~

~~Dimethicone Copolyol as an ingredient name has been deleted from the *International Cosmetic Ingredient Dictionary and Handbook* and replaced with several ingredients that adhere to the former definition of Dimethicone Copolyol as "a polymer of dimethylsiloxane with polyoxyethylene and/or polyoxypropylene side chains" (Pepe et al. 2002).~~

~~The new ingredients that are described by this definition include: Dimethicone PEG-7 Phosphate, Dimethicone PEG-10 Phosphate, Dimethicone PEG/PPG-7/4 Phosphate, Dimethicone PEG/PPG-12/4 Phosphate, Dimethicone PEG/PPG-20/23 Benzoate, Dimethicone PEG-8 Benzoate, Dimethicone PEG-6 Acetate, Dimethicone PEG-8 Adipate, PEG-3 Dimethicone, PEG-9 Dimethicone, PEG/PPG-20/29 Dimethicone,~~

International Journal of Toxicology
2017, Vol. 36(Supplement 2) 44S-45S

DOI: 10.1177/1091581817716148
journals.sagepub.com/home/ijt
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Dibutyl, Dimethyl, and Diethyl Phthalate and Butyl Benzyl Phthalate

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Keywords
phthalates, safety, cosmetics

Conclusion

In a 1985 safety assessment of dibutyl, diethyl, and dimethyl phthalate, the Cosmetic Ingredient Review Expert Panel stated that these ingredients are safe for use in cosmetics in the present practice of use and concentration.[1] Subsequently, in 2005, the Panel conducted an extensive rereview of the newly available studies since that assessment, confirmed the decision, and determined to not reopen that report.[2] In 1992, butyl benzyl phthalate was found safe in the present practice of use and concentration.[3] The Panel reviewed studies performed since that assessment as well as updated the use and concentration data in 2007 and confirmed that conclusion.[4] In 2012, the Panel reviewed 3 new studies on phthalates published in 2012 and confirmed that dibutyl, dimethyl, and diethyl phthalate and butyl benzyl phthalate are safe in cosmetics in the present practices of use and concentration. The Panel did not reopen the safety assessment.

Discussion

The Panel reviewed new studies that focused on the potential for endocrine disruption/reproductive and developmental toxicity on dibutyl, dimethyl, and diethyl phthalate and butyl benzyl phthalate. One study of children aged 5 to 9, who were part of a Manhattan-Bronx cohort, revealed detectable, although varied, levels of phthalates in the urine of all 244 study participants.[5] Higher levels of both diethyl phthalate and butyl benzyl phthalate were associated with airway inflammation.

Two studies addressed diabetes and phthalates. In 1 study, there were 1,015 men and women 70 years of age from Uppsala, Sweden.[6] One sample per participant was collected from 2001 to 2004 and analyzed 5 to 8 years later. In this study, blood levels for dimethyl phthalate, diethyl phthalate, diisobutyl phthalate, and diethylhexyl phthalate were measured and correlated with measures of insulin resistance and poor insulin secretion in nondiabetic participants.

In the second study, urinary concentrations of phthalate metabolites measured by the Centers for Disease Control and Prevention and self-reported diabetes in 2,350 women aged 20 to <80 participating in the National Health and Nutrition Examination Survey (NHANES) (2001-2008) were used.[7] The odds ratio for diabetes in women with higher levels of n-butyl phthalate, isobutyl phthalate, benzyl phthalate, 3-carboxypropyl phthalate, and the sum of diethylhexyl phthalate metabolites was greater than the odds ratio for women with the lowest concentrations of these phthalates.

The Panel noted that all of these studies identified associations between phthalate metabolites and either diabetes or airway inflammation. Such studies did not suggest a causal link between phthalates and any adverse outcome. The possibility that phthalate metabolites may impact peroxisome proliferation pathways was suggested in the diabetes studies, but that mechanism is not established as a mode of action. The Panel agreed that that there is a need for further study of the reported association between phthalates exposures and diabetes and to investigate possible causal links.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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