DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

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Date: May 2, 2000

From: Division of Product Manufacture and Use
Chemistry and Exposure Assessment Team, HFS-246

Subject: FAP 9Z4681 (MATS #1070 M2.0 and 2.1): National Environmental Trust; submission of 5/13/99. Migration of di(2-ethylhexyl) adipate from polyvinyl chloride cling film and bisphenol-A from can coatings and polycarbonate baby bottles and tableware.

To: Division of Petition Control, HFS-215
Attn: J. Smith

The National Environmental Trust (NET) has submitted recent literature data on the migration into food of di(2-ethylhexyl) adipate (DEHA) from polyvinyl chloride (PVC) cling film and bisphenol-A (BPA) from can coatings and polycarbonate (PC) baby bottles and tableware. The NET provided brief analyses of the literature data and attempted to make conclusions about consumer exposure to DEHA and BPA based on these data in order to support its request that FDA amend the existing food additive regulations to restrict the use of these and other substances that were listed as "Chemicals Suspected of Having Endocrine Disrupting Effects" by the Japanese Environment Agency's Strategic Programs on Environmental Endocrine Disrupters (SPEED) in May 1998.

We will not comment further on issues raised in the petition relating to the definition of "generally recognized as safe" (GRAS) or to proposed changes to the Federal Food, Drug, and Cosmetic Act and 21 *CFR*. The following is our analysis of the literature data submitted by NET within the context of our current exposure estimates for DEHA and BPA.

DEHA

DEHA is currently regulated in 21 *CFR* 178.3740 (Plasticizers in polymeric substances) for use as a plasticizer in polymeric substances at a level not to exceed that reasonably required to accomplish the intended technical effect.[1] In the U.S., DEHA is used as a plasticizer in PVC food-contact films at levels of 15 to 22.5 wt-% of the film.[2] In response to a 6/5/98 submission from Consumers Union (CU),[3] we collected extensive literature data on DEHA

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[1] DEHA is also regulated in §175.105 (Adhesives), §177.200 (Cellophane), §177.1400 (Water-insoluble hydroxyethyl cellulose films), and §177.1210 (Closures with sealing gaskets for food containers).

[2] Society for the Plastics Industry through Keller and Heckman, "Report on Plasticizers Used in Food-Contact Films," December 1991, pp. 3-20, 23-26, Table 1 on pp. 28-30. In FAP 1T3573, Vol. 40, pp. 15798-15815, 15818-15821, Table 1 on pp. 15823-15825.

[3] See CTS# 59579, Consumers Union, "Migration of plasticizers from flexible packaging into

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concentrations in foods that are typically wrapped in PVC cling film and, on 4/19/99, calculated a total estimated daily intake (EDI) of 7.3 mg/person/day (2.4 ppm dietary concentration).[4] We also calculated the EDI for DEHA strictly from cheese consumption to be 0.26 mg/person/day (87 ppb dietary concentration).[4] We have high confidence in these exposure values because 1) they were based on a large database of DEHA migration data, which enabled us to use average migration values for most of the food types, and 2) we were able to develop food-type distribution factors for several subtypes of food, using per-capita consumption data from the USDA Nationwide Food Consumption Survey,[5] which allowed us to match migration data to very specific food types.

NET stated on p. 3 of the petition that "numerous studies have confirmed that DEHA can leach out of plastic wrap into food" and listed 7 studies to support this statement. We included data on DEHA concentrations in food from 6 of these studies, as well as 5 additional studies, in our 4/19/99 exposure estimate.[4] We did not include data from the Petersen (1995) study because the PVC cling film used in that study contained a polymeric plasticizer in addition to DEHA.[6] Polymeric plasticizers such as triisobutyl citrate are not used in PVC cling film produced in the U.S.[7] However, since the late 1980s, they have been used in PVC cling film produced in the UK to reduce the exposure to DEHA from food.[8,9]

On p. 4 of the petition, NET reported the results CU obtained from its analyses of cheese wrapped in various types of plastic film. We evaluated these same data in detail and determined that the total levels of DEHA in CU's 6 cheese samples that were packaged in direct contact with PVC cling film ranged from 51 to 270 mg/kg with an average of 139 mg/kg.[3] We found that these values agreed very well with values reported in the literature for cheese wrapped in PVC cling film of the type used in the U.S. and included them in our 4/19/99 exposure estimates for DEHA.[4]

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cheese, especially di(2-ethylhexyl) adipate from polyvinyl chloride cling film," memorandum dated 3/8/99, K. Paquette (HFS-246) to V. Anand (HFS-215).

[4] FAP 1T3573, "Recalculation of exposure to di(2-ethylhexyl) adipate plasticizer from foods wrapped in polyvinyl chloride cling film," memorandum dated 4/19/99, K. Paquette (HFS-246) to V. Anand (HFS-215).

[5] TASDIET Ver. 3.5.1, International Diet Research System, Technical Assessment Systems, Inc., 1997. Based on USDA Nationwide Food Consumption Survey, 1988-1991 combined data.

[6] Petersen, J.H., E.T. Naamansen, and P.A. Nielsen, "PVC Cling Film in Contact with Cheese: Health Aspects Related to Global Migration and Specific Migration of DEHA," *Food Additives and Contaminants*, Vol. 12, No. 2, 1995, pp. 245-253.

[7] At a meeting between the Chemical Manufacturers Association (CMA) and FDA on 7/22/98, CMA representatives stated that polymeric plasticizer replacements for DEHA have not been regulated for food-contact use in the U.S. [redacted]

[8] "Plasticizers: Continuing Surveillance," Food Surveillance Paper No. 30, Ministry of Agriculture, Fisheries and Food (MAFF), London: HMSO, 1990.

[9] "Survey of Plasticiser Levels in Food Contact Materials and in Foods," Food Surveillance Paper No. 21, Ministry of Agriculture, Fisheries and Food (MAFF), London: HMSO, 1987.

We cannot emphasize enough, however, that, although the DEHA levels in PVC-wrapped cheese appear to be high, only a small fraction of retail cheese is wrapped in PVC cling film.[3] In FDA's 1998 Total Diet Survey, 15 samples representative of cheeses available for purchase in the U.S. were collected nationwide for analysis. None of these samples was packaged in PVC film.[10] Similarly, none of the cheese samples collected in June 1986 for the Canadian Total Diet Program was packaged in PVC film.[11] Use of PVC film appears to be declining and is primarily used in retail outlets where the cheese is wrapped at the point of sale.[12] It is therefore highly unlikely that a child would consume all of its daily cheese from that wrapped in PVC cling film, particularly since the singles-type cheese often consumed by children is wrapped in plastics such as polypropylene (PP) or high-density polyethylene (HDPE) that do not require plasticizers.[3]

NET's attempt on p. 4 of the petition to apply our "threshold of regulatory concern" of 0.5 ppb to DEHA levels in cheese is misguided for two reasons. 1) Apparently, NET does not understand the difference between dietary concentration and the concentration of an additive in food. We apply consumption factors and food-type distribution factors to concentrations of additives in food to obtain a more realistic amount of an additive that is expected be in an individual's daily diet, i.e., the dietary concentration. We suggest that NET be sent a copy of our "Recommendations,"[13] which contains a detailed description of how the dietary concentration is calculated. 2) Our threshold of regulatory concern does not apply to substances that are the subject of food additive petitions (FAP) or food contact notices (FCN). By definition, substances that are the subject of FAPs or FCNs may have dietary concentrations greater than 0.5 ppb. DEHA was the subject of a food additive petition when it was first regulated for food-contact use, so it received the toxicological scrutiny required for the specific exposure determined for it.

NET stated on p. 4 of the petition that the Society of the Plastics Industry (SPI) calculated a much lower "average daily dose" from cheese consumption than did CU, although both were based on comparable migration data.[2,3] The reason for the disparity in SPI's and CU's "exposure" values is that SPI's value was reported as a dietary concentration, and CU's was reported as a concentration in cheese.

NET did not provide any new migration- or exposure-related data for DEHA in the subject submission that were not already included in our 4/19/99 exposure evaluation. Therefore, we see no reason to change our 4/19/99 exposure calculation for DEHA.

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[10] "Plasticizers Determined in Cheese Wraps from Total Diet Survey," communication sent by Tim Begley (HFS-245) to K. Paquette (HFS-246), 2/4/99.

[11] Page, D.B. and G. LaCroix, "The Occurrence of Phthalate Ester and Di-2-ethylhexyl Adipate Plasticizers in Canadian Packaging and Food Sampled in 1985-1989: A Survey," Food Additives and Contaminants, Vol. 12, No. 1, 1995, pp. 129-151.

[12] Castle, L., A.J. Mercer, J.R. Startin, and J. Gilbert, "Migration from Plasticized Films into Foods. 2. Migration of Di-(2-ethylhexyl)adipate from PVC Films Used for Retail Food Packaging," *Food Additives and Contaminants*, Vol. 4, No. 4, 1987, pp. 399-406.

[13] "Recommendations for Chemistry Data for Indirect Food Additive Petitions," Chemistry Review Branch, Center for Food Safety and Applied Nutrition, FDA, June 1995.

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BISPHENOL-A

BPA (4,4'-isopropylidene diphenol) is currently regulated for use as a monomer in the manufacture of PC (§177.1580 Polycarbonate resins) and in the manufacture of epoxy polymer resins, including those used in food-contact can enamels (§175.300 Resinous and polymeric coatings). In a 3/13/96 evaluation of adult and infant exposure to BPA from PC articles and can enamels, we calculated an EDI for adults of 11 μg/person/day (3.7 ppb dietary concentration) and an EDI for infants of 7 μg/person/day (8.3 ppb dietary concentration).[14] BPA migration data from several studies, including two that were later published by the FDA,[15,16] were included in our exposure estimate.[17,18] For the adult exposure estimate, we used our traditional approach of applying consumption factors and food-type distribution factors for PC articles and epoxy-coated cans to the migration data to obtain the dietary concentration. For the infant exposure estimate, we used detailed information from the literature on the length of time infants consume formula and mean average-daily-consumption data for infant formula from the USDA Continuing Survey of Food Intake by Individuals[19] to obtain a realistic value.

FDA Article on BPA Migration from PC Baby Bottles

On p. 6 of the petition, NET provided a brief discussion of FDA's article on BPA migration from PC baby bottles.[15] This article described several migration tests that were conducted with cut-up bottle strips (2-sided migration) or intact bottles (1-sided migration) in contact with various food simulants (water; 8%, 10%, 50%, or 95% ethanol; Miglyol 812) or real foods (infant formula or juice) under various time and temperature conditions. Only two of the tests simulated *normal use* of the baby bottles: 1) Intact bottles were held in boiling water for 5 min., filled with apple juice or formula, and refrigerated at 4° C for 24 hrs. BPA was not detected in the juice or formula at a limit of detection (LOD) of 100 ng/mL (100 ppb). 2) Bottle pieces were placed in the food simulants, heated at 100° C for 30 min., and refrigerated

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[14] See "Cumulative exposure estimates for bisphenol-A (BPA), individually for adults and infants, from its use in epoxy-based can coatings and polycarbonate (PC) articles," memorandum dated 3/13/96, A. Bailey (HFS-247) to G. Diachenko (HFS-245).

[15] Biles, J.E., T.P. McNeal, T.H. Begley, and H.C. Hollifield, "Determination of Bisphenol-A in Reusable Polycarbonate Food-Contact Plastics and Migration to Food-Simulating Liquids, *Journal of Agricultural and Food Chemistry*, Vol. 45, No. 9, 1997, pp. 3541-3544.

[16] Biles, J.E., T.P. McNeal, and T.H. Begley, "Determination of Bisphenol A Migrating from Epoxy Can Coatings to Infant Formula Liquid Concentrates," *Journal of Agricultural and Food Chemistry*, Vol. 45, 1997, pp. 4697-4700.

[17] Brotons, J.A., M.F. Olea-Serrano, M. Villalobos, V. Pedraza, and N. Olea, "Xenoestrogens Released from Lacquer Coatings in Food Cans," *Environmental Health Perspectives*, Vol. 103, 1995, pp. 609-612.

[18] Epoxy Resin Can Coating Work Group, Society for the Plastics Industry Inter-Industry Group on Bisphenol A and Alkyl Phenols (SPI-IGBAP), "Report on Potential Exposure to Bisphenol A from Epoxy Can Coatings," September 1995. In FMF 580.

[19] TASDIET Ver. 3.14, International Diet Research System, Technical Assessment Systems, Inc. Based on the combined 1989-90, 1990-91, and 1991-92 USDA Continuing Survey of Food Intake by Individuals (CSFII) survey data.

for 72 hrs. The BPA level in the 10% ethanol and water food simulants was 2 μg/kg (2 ppb), after correction for the food mass-to-surface area typical of baby bottles. The LOD for BPA in these simulants was 2 ng/mL (2 ppb). The higher LOD for BPA in juice and formula (by 2 orders of magnitude, not 6 as NET claimed) was due to matrix effects of the real foods. It has historically been shown that migration into food simulants is exaggerated over that which is observed in real foods. We therefore used the 2 μg/kg migration value from experiment 2 above in our calculation of infant exposure to BPA.

The temperature conditions used in experiment 2 above exaggerate the intended use of PC baby bottles. Manufacturers of PC baby bottles clearly state in the instructions that accompany new PC bottles that formula is not to be heated in the bottle. The formula is to be heated separately and then poured into the bottle before it is fed to infants.

On p. 6 of the petition, NET cited a *Chemical Week* article that stated, "About 5% of unreacted bisphenol A leaches out of polycarbonate baby bottles when they are subjected to normal stove-top heating, according to FDA researchers."[20] This statement is highly misleading because there is no such thing as "normal stovetop heating" of formula in PC baby bottles. As was discussed above, formula is not intended to be heated in PC bottles. However, the FDA migration test upon which we relied to calculate infant exposure to BPA from PC bottles did involve heating PC strips in food simulants at 100° C for 30 min. to obtain conservative migration values (see experiment 2 above). Even under these exaggerated conditions, the migration was still extremely low (2 μg/kg in food).

The FDA did observe a 5% loss of residual BPA in the first cycle of an experiment that was conducted to provide information on BPA migration over several use cycles of PC baby bottles.[15] In this case, PC baby bottle strips in 10% ethanol food simulant were heated at 100° C for 30 min. and allowed to cool to room temperature, and the food simulant was analyzed for BPA. This process was repeated several times with fresh simulant to track BPA migration during an exaggerated repeat-use scenario. Although the conditions for each cycle were similar to those used in experiment 2 above, residual BPA losses in experiment 2 were much lower than 5%. The reason for this discrepancy is likely the fact that ethanol is an aggressive solvent for PC polymer.[21] At low ethanol concentrations, low temperatures, and short duration, the migration of BPA from PC is similar to that into water (see Table 3 in reference 15). However, if one or more of these variables is increased, the ethanol can degrade the PC, resulting in highly variable migration results.

Consumers Union (1999) Migration Tests

On p. 7 of the petition, NET provided results of migration tests done by CU to determine the amount of BPA that migrates from PC baby bottles. NET stated that CU placed strips cut from PC baby bottles into a "formula simulant" (not further identified), heated the samples at 95° C for 30 min., and analyzed the simulant for BPA. NET reported that CU found approximately 1 ppb (1 μg/kg) BPA in the samples. According to NET, CU also filled a

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[20] "FDA on Bisphenol A," *Chemical Week*, October 29, 1997, p. 46.
[21] Conversation between J. Biles (HFS-245) and K. Paquette (HFS-246), 4/24/00.

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single intact baby bottle with "formula simulant" and found 1 ppb (1 μg/kg) BPA in the simulant (no further details given).

Unfortunately, the reference NET gave for the CU migration experiments did not include any experimental details or quantitative results.[22] The reference simply stated that CU had heated plastic from 6 baby bottles in simulated infant formula and that BPA leached into the test formula. The reference also stated that the test with the intact bottle resulted in a BPA exposure that is 4% of an amount that adversely affected test animals in studies done by Frederick vom Saal (apparently 2 μg/kg (ppb) body weight of female rats; see p. 8 of the petition). This statement does not provide any useful quantitative information since we do not know how CU calculated exposure or compared 1 μg/kg BPA in food to 2 μg/kg body weight of female rats. We therefore cannot verify NET's report of CU's migration test results.

However, we can conclude that the BPA levels reported to be found by CU in the infant formula simulant (≈ 1 μg/kg) did not differ from that determined by FDA for exaggerated normal use conditions (2 μg/kg).[15]

Takao (1999) Article on BPA Migration

On p. 7 of the petition, NET provided a detailed discussion of BPA migration tests done by Takao *et al.* (1999) on PC baby bottles and tableware (apparently soup bowls) used in Japanese elementary schools, as well as determinations of BPA in foods and beverages stored in epoxy-coated cans.[23] However, the published article consisted of only one page and did not provide nearly the detail presented by NET in the petition. We cannot comment on unsupported data provided by NET. The published article provided the following BPA levels in food simulants or food without any information on the number of samples analyzed or any statistical treatment of the results:

Article	Food Simulant or Food/ Conditions	BPA Concentration in Food, μg/kg
PC baby bottle (new)	Water / 95° C, 30 min.	<1.0 to 3.5
PC baby bottle (used)	Water / 95° C, 30 min.	<1.0 to 6.5
PC tableware (new) used in Japanese elementary schools	Water / 95° C, 30 min.	1.0 to 1.9
PC tableware (used) used in Japanese elementary schools	Water / 95° C, 30 min.	1.8 to 7.9
Epoxy-coated can	Coffee / not specified	89.6 to 127.1
Epoxy-coated can	Oolong tea / not specified	7.2 to 8.0
Epoxy-coated can	Soft drink / not specified	<1.0

[22] "Baby Alert: New Findings About Plastics," *Consumer Reports*, May 1999, pp. 28-29.
[23] Takao, Y., H.C. Lee, Y. Ishibashi, S. Kohra, N. Tominaga, and K. Arizono, "Fast Screening Method for Bisphenol A in Environmental Water and in Food by Solid-Phase Microextraction (SPME)," *Journal of Health Science*, Vol. 45, 1999, p. 39.

The migration of BPA from new and used PC baby bottles determined by Takao *et al.* is comparable to that determined by FDA under exaggerated normal use conditions (2 μg/kg in food). PC tableware such as bowls is not widely used in the U.S. and is limited to use primarily by children, but not on the same scale at which PC baby bottles are used by infants. We do not currently have market data on PC tableware and therefore cannot calculate a specific exposure to BPA from these items. However, children's exposure to BPA from PC tableware is likely to be extremely small. The fact that BPA migration from PC tableware is comparable to that from PC baby bottles indicates that children's exposure to BPA from PC tableware is likely covered by the conservatisms built into our BPA exposure estimate for infants.

The levels of BPA determined by Takao *et al.* in foods packaged in epoxy-coated cans are comparable to the levels in canned foods used in our BPA exposure estimate for adults.[14]

Iguchi (1998) Report on BPA Migration

On pp. 7-8 of the petition, NET provided a summary of BPA migration tests done on PC bowls by Iguchi at Yokohama City University, Japan. Unfortunately, this work has not been published, nor has NET been able to provide us raw data, a manuscript, or a copy of slides from a formal presentation of this work. Apparently, NET received this information verbally from Iguchi via an informal presentation or personal communication. As was mentioned above, we cannot comment on unsupported, anecdotal data.

NET provided three new studies on the migration of BPA from PC articles and epoxy-coated cans into food that were not included in our 3/13/96 exposure estimate. Of these studies, only the Takao study included data that had been published and peer reviewed. Nevertheless, our analysis of the Takao data and NET's summary of the CU data indicates that these migration data are comparable to those used in our exposure estimate. We therefore see no reason to change our 3/13/96 exposure estimate for BPA.

CONCLUSIONS

In the subject petition, NET made several incorrect interpretations of literature data on the migration to food of DEHA from PVC cling film and of BPA from PC articles and epoxy-coated cans. We have addressed each of these errors and described our exposure estimates for these additives in an effort to educate NET about FDA's method for assessing exposure to indirect food additives.

NET did not provide any new migration- or exposure-related data for DEHA in the subject submission that were not already included in our 4/19/99 exposure evaluation. Therefore, we see no reason to change our 4/19/99 exposure calculation for DEHA: total EDI of 7.3 mg/person/day (2.4 ppm dietary concentration); EDI strictly from cheese consumption of 0.26 mg/person/day (87 ppb dietary concentration).

In the case of BPA, NET provided three new migration studies that had not been included in our 3/13/96 exposure estimate. Only one of these studies included data that had been

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published and peer reviewed (Takao, 1999). We could not consider one of the studies (Iguchi, 1998) because NET provided only a brief summary without any supporting data from the author. Nevertheless, our analysis of the Takao data and NET's summary of the CU data indicates that these migration data are comparable to those used in our exposure estimate. We therefore see no reason to change our 3/13/96 exposure estimate for BPA: EDI for adults of 11 μg/person/day (3.7 ppb dietary concentration); EDI for infants of 7 μg/person/day (8.3 ppb dietary concentration).

NET did not provide any migration- or exposure-related data for any of the other substances included in the Japanese SPEED list that are currently regulated as food additives, GRAS substances, or prior sanctioned substances. We therefore do not see any reason to revise our current exposure estimates for these substances.

Kristina E. Paquette, Ph.D.

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