Steward, Kara (ECY)

From: Nancy Uding <nuding@toxicfreefuture.org>
Sent: Friday, October 14, 2016 4:18 PM
To: Steward, Kara (ECY)
Cc: Erika Schreder; Laurie Valeriano
Subject: Additional info on phthalates for CSPA rule
Attachments: DNPP 131-18-0 Support Info.docx; DIOP 27554-26-3 Support Info.docx; DIBP 84-69-5 Support Info.docx; DEMP 117-82-8 Support Info.docx; DCHP 84-61-7 Support Info.docx

Kara,
Please find attached five documents with additional information on phthalates Toxic-Free Future is asking Dept. of Ecology to add to the CHCC reporting list. We are working on one additional phthalate and will send that to you next week.
Thank you,
Nancy Uding

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Nancy Uding | Grants and Research

Toxic-Free Future

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Bis (2-methoxyethyl phthalate) (DEMP) (CAS # 117-82-8)

Use: Bis (2-methoxyethyl phthalate) (DEMP) is used as a plasticizer in cellulosic resins, some vinyl ester resins, PVC, and as a solvent, a molding component in adhesives, and laminating cements. [1].

Children's exposure: DEMP can be present at up to 40% (possibly in combination with other phthalates) in toys, including inflatable water products, hoppers, play and exercise balls according to Australian industry sources [2]. In children's toys and childcare articles made from polyvinyl chloride (PVC), DEMP may also be used as a secondary plasticizer or be present as a contaminant [2]. DEMP was detected in indoor dust in Hamburg, Germany, between 1998 and 2000 [3]. It was also detected in indoor air in Australia[3]. DEMP was detected in Germany in T-shirts (10–30 µg/kg), diapers (10–20 µg/kg) and house carpets (10–50 µg/kg) [4].

Toxicity:

DEMP is found on the following authoritative lists:

- EU REACH Candidate List of Substances of Very High Concern for Authorisation (SVHC list). Reason for listing: Toxic for Reproduction [5].
- EU – Annex VI CMRs: Reproductive Toxicity Category 1B[6].
- EU R-phrases: R61 May cause harm to the unborn child [6].
- EU R-phrases: R62 Possible risk of impaired fertility [6].
- EU GHS H-statements: H360Df – May damage the unborn child. Suspected of damaging fertility.
- EU – REACH Annex XVII CMRs: Repr. Categrory 1B [7].

Reproductive Toxicity: In an oral exposure (gavage) repeated dose study in Sprague-Dawley rats DEHP metabolite 2-methoxyethanol (2-ME) was reported to have an LOAEL of 100 mg/kg bw-day for degeneration of spermatocytes, and an LOAEL of 250 mg/kg bw-day for decreased relative testis weight, seminal tube atrophy and sperm degeneration [2]. In two DEMP oral exposure by gavage studies in rats an LOAEL of 1000 mg/kg bw-day was reported for decreased testes weight and an LOAEL of 1000 mg/kg bw-day was reported for decreased testes weight and abnormal sperm heads [2]. In a study on oral exposure of Sprague-Dawley rats to DEMP metabolite methoxyacetic acid (MAA) an LOAEL of 592 mg/kg bw-day was reported for decreased testes weight, however this was the lowest dose tested [2].

Developmental Toxicity: In a study in which Wistar rats were exposed to DEMP metabolite 2-methoxyethanol (2-ME) orally by gavage an LOAEL of 158 mg/kg bw-day was reported for the effect of increased fetal resorptions and increased gross and skeletal malformations [2]. In another study in which female monkeys were exposed to 2-ME orally by gavage an LOAEL of 12 mg/kg bw-day was reported for increased intrauterine death with 100% intrauterine death at 36 mg/kg/bw-day [2]. In a study in which Sprague-Dawley rates were exposed orally by gavage to DEMP metabolite MAA an LOAEL of 187 mg/kg bw-day was reported for increased fetal resorptions and increased gross and skeletal malformations [2]. Developmental effects of DEMP were observed in rats following oral (gavage) administration on gestation days 6 to 16. Significantly reduced pup body weight gain and slightly reduced pup survival were observed at the lowest dose tested (60 mg/kg-bw per day, LOAEL). At a higher dose level (180 mg/kg-bw per day), significantly reduced pup survival and pup body weight gain as well as pup abnormalities, including a shortened lumbosacral region, acauda and filamentous tails, were observed[4].

1. United States Consumer Product Safety Commission (CPSC), 2011. Memorandum: CPSC Staff Toxicity Review of Two Phthalates and One Phthalate Alternative for Consideration by the Chronic Hazard Advisory Panel.
2. Australia National Industrial Chemicals Notification and Assessment Scheme (NICNAS), 2016. Di(methoxyethyl) phthalate (DMEP), Existing chemical info sheets. https://www.nicnas.gov.au/communications/publications/informationsheets/existingchemicalinfosheets/dimethoxyethylphthalatedmp.
3. BAuA Federal Institute for Occupational Safety and Health, Federal Office for Chemicals, Dortmund, Germany. Annex XV Dossier: Proposal for Identification of a Substance as a CMR (1A or 1BG), PBT, vPvB or a Substance of an Equivalent Level of Concern, Substance Name: Bis(2-methoxyethyl)phthalate, CAS Number 117-82-8.
4. Environment Canada, Health Canada, 2009. Screening Assessment for the Challenge; 1,2-Benzenedicarboxylic acid, bis(2-methoxyethyl) ester, Chemical Abstracts Service Registry Number 117-82-8.
5. ECHA Candidate List of substances of very high concern for authorisation (SVHC). http://echa.europa.eu/candidate-list-table.
6. ECHA Substance Information, Bis (2-methoxyethyl phthalate) (DEMP) CAS # 117-82-8. Summary of Classification and Labelling, https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/15512, retrieved 10/11/16.
7. ECHA European Chemicals Agency, Table of harmonized entries in Annex VI to CLP. Annex VI to CLP spreadsheet, retrieved 10/12/16.

Dicyclohexyl phthalate (DCHP) (CAS # 84-61-7)

Use: Dicyclohexyl phthalate (DCHP) is used in the manufacture of plastisol which is used in sealant compounds and textile printing, is used as a co-plasticizer in manufacturing PVC, rubber, and plastic compounds, and is used in the formulation of organic peroxide as a phlegmatizer and dispersing agent [1]. DCHP is included in fabrics, textiles, and apparel, and in plastic articles [1,2]. It is used in screen printing inks [2].

Children's Exposure: In the US, DCHP has been found in bar soap, modeling clay (4000 mg/kg), pajamas (3400 mg/kg), and perfume (3 mg/kg) in 1 of 36 perfume samples [1]. DCHP was found in household dust in Kuwait (median 2.9 µg/g). An exposure estimate of daily DCHP intake from the dust indicated that toddler's exposure was 9 fold higher than that of adult's. DCHP was found in household dust in China and USA (upper limit of 0.3 µg/g) at a frequency of 15% and 18%, respectively. DCHP was found in indoor air in Norway (4 – 5 ng/m^3). DCHP was found in indoor air samples in Tokyo (0.07 µg/m^3). Exposure to dicyclohexyl phthalate can occur via inhalation of ambient air, ingestion of food and beverages, and dermal contact with consumer products containing it[3].

Toxicity:

DCHP is found on the following authoritative lists:

- EU – Annex VI CMRs: Reproductive Toxicity Category 1B [4].
- EU – REACH Annex XVII CMRs – Reproductive Toxicity Category 1B [4].
- EU GHS H-statements: H360D May damage the unborn child [4].
- EU Priority Endocrine Disruptor Group III [5].

Reproductive and Developmental Toxicity: In a key oral DCHP exposure study the most sensitive endpoints were lowered prostate weight, reduced anogenital distance and retained areola mammae in rats (LOAEL 80-107 mg/kg bw/day, NOAEL 16-21 mg/kg bw/day) [1]. In another study DCHP exposure in utero (0, 20, 100 and 500 mg/kg bw/day) resulted in an increased number of litters with resorptions at all doses, in a decrease in male fetal pup anogenital distances, and in increased inhibin B levels in all dose groups. Testosterone and anti-Mullerian hormone (AMH/MIS), as well as the follicle stimulating hormone (FSH) to Inhibin B ratio decreased in the mid-and high dose group. Histopathological effects in the testes were also evident in a dose dependent manner [1]. In another study histopathological changes were observed in testes, epididymis and prostate at all dose levels with a LOAEL of 20 mg/kg bw/day. The percentage of abnormal epididymal sperm was significantly increased at all doses (0, 20, 100 and 500 mg/kg/day) in the adult animals [1].

Endocrine Activity: The overall weight of evidence analysis shows that the male reproductive effects observed following in utero exposure to DCHP are mediated via an endocrine (antiandrogenic) mode of action that involves irreversible effects induced by interference with steroidogenesis during fetal development [1].

Additional Considerations: The Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives (CHAP) recommended to the U.S. Product Safety Commission in July, 2014 that DCHP should be permanently banned from use in children's toys and child care articles at levels greater than 0.1 % [6]. DCHP is on EPA's TSCA Work Plan List, however the hazard criteria met for inclusion on this list is DCHP's acute and chronic aquatic toxicity [7].

1. European Chemicals Agency (ECHA), Sweden and Denmark, 2015. Annex XV Report: Proposal for Identification of a Substance of Very High Concern on the Basis of the Criteria Set Out in REACH Article 57 Substance Name(s): Dicyclohexyl phthalate (DCHP) EC Number(s): 201-545-9 CAS Number(s): 84-61-7, http://echa.europa.eu/documents/10162/b2fbb22c-72d7-491d-b417-39105e35b792.
2. Australian Government Department of Health and Aging, NICNAS, 2008. Existing Chemical Hazard Assessment Report Dicyclohexyl Phthalate.
3. Toxnet Hazardous Substances Data Bank (HSDB): Dicyclohexyl phthalate, RN 84-61-7, http://toxnet.nlm.hih.gov, retrieved 10/13/16.
4. ECHA European Chemicals Agency, Table of harmonized entries in Annex VI to CLP. Annex VI to CLP spreadsheet, retrieved 10/13/16.
5. European Commission DG ENV, 2000. Towards the establishment of a priority list of substances for further evaluation of their role in endocrine disruption – preparation of a candidate list of substances as a basis for priority setting, Final Report, Annex I. http://ec.europa.eu/environment/chemicals/endocrine/strategy/substances_en.htm#priority_list
6. Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives (CHAP), July, 2014. Report to the U.S. Consumer Product Safety Commission Directorate for Health Services.
7. U.S. Environmental Protection Agency, 2014. TSCA Work Plan for Chemical Assessments: 2014 Update. https://www.epa.gov/sites/production/files/2015-01/documents/tsca_work_plan_chemicals_2014_update-final.pdf

Dipentyl phthalate (DNPP or DPENP) or Di-n-pentyl phthalate (CAS # 131-18-0)

Use: Dipentyl phthalate (DNPP) is used as a plasticizer in PVC[1].

Children's Exposure: DNPP was detected in 8 out of 10 samples of house dust in Austria[1]. The general population may be exposed via dermal contact with consumer products such as textiles, paper or paints containing DNPP [1]. The DNPP metabolite MHPP has been detected in human urine (29% of people sampled) [2].

Toxicity:

DNPP is found on the following authoritative lists:

- EU REACH Candidate List of Substances of Very High Concern for Authorization (SVHC list). Reason for listing: Toxic for Reproduction [3].
- EU – Annex VI CMRs: Reproductive Toxicity Category 1B [4].
- EU R-phrases: R61 May cause harm to the unborn child [4].
- EU R-phrases: R60 May impair fertility [4].
- EU GHS H-statements: H360FD May damage fertility, may damage the unborn child [4].

Reproductive and Developmental Toxicity: In one study pregnant Sprague-Dawley rats were treated by gavage daily from gestational days 12 – 19 with corn oil (control) or with 500 mg/kg per day dipentyl phthaltate (DNPP) (treatment). Anogenital distances were significantly reduced in male fetuses exposed to DNPP. DNPP exposure also significantly altered expression of 391 genes that affect molecular pathways in testicular development [5]. In another study pregnant female Sprague-Dawley rats were dosed by gavage with either corn oil (control) or doses of 25, 50, 100, 200, 300, 600, and 900 mg/kg/day during gestation days 8 – 18. Midgestation pregnancy loss leading to 100% fetal mortality was experienced by dams given doses of 300, 600, and 900 mg/kg/day DNPP. The NOAEL for reproductive and maternal effects was 200 mg/kg/day while the LOAEL was 300 mg/kg/day with 100% fetal mortality. DNPP reduced fetal testosterone production at doses as low as 100 mg/kg/day [6].

Additional Considerations: The Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives (CHAP) recommended to the U.S. Product Safety Commission in July, 2014 that DNPP should be permanently banned from use in children's toys and child care articles at levels greater than 0.1% [7]. The CHAP also describes DNPP as among the most potent phthalates regarding developmental effects, that the toxicological profile of DPENP is very similar to that of the other antiandrogenic phthalates, and that DNPP exposure contributes to the cumulative risk [7].

1. Bureau for Chemical Substances, Poland, 2013. Annex XV Dossier, Proposal for Identification of a Substance As A CMR 1A or 1B, PBT, vPvP Or A Substance Of An Equivalent Level of Concern: Dipentyl Phthalate (DPP) EC Number: 205-017-0, CAS Number: 131-18-0.
2. Silva, MJ, Furr, J, Samandar, E, Preau, JL, Gray, LE, Needham, LL, and Calafat, AM (2011). Urinary and serum metabolites of di-*n*-pentyl phthalate in rats. Chemosphere 82: 431-436.
3. ECHA Candidate List of substances of very high concern for authorisation (SVHC). http://echa.europa.eu/candidate-list-table.
4. ECHA Substance Information, Dipentyl phthalate CAS # 131-18-0, Summary of Classification and Labelling, https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/68860, retrieved 10/11/16.

5. Liu, K, Lehmann, KP, Sar, M, Young, SS, and KW Gaido. 2005. Gene expression profiling following in utero exposure to phthalate esters reveals new gene targets in the etiology of testicular dysgenesis. Biology of Reproduction 73: 180-192.
6. Howdeshell, KL, Wilson, VS, Furr, J, Lambright, CR, Rider, CV, Blystone, CR, Hotchkiss, AK, and LE Gray. 2008. A mixture of five phthalate esters inhibits fetal testicular testosterone production in the Sprague-Dawley rat in a cumulative, dose-additive manner. Toxicological Sciences 105(1): 153-165.
7. Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives (CHAP), July, 2014. Report to the U.S. Consumer Product Safety Commission Directorate for Health Services.

Diisobutyl phthalate (DIBP) (CAS # 84-69-5)

Use: DiBP is considered a specialty plasticizer and is often combined with other phthalates. It has been used as a plasticizer for PVC, nitrocellulose, cellulose ether, and polyacrylate and polyacetate dispersions. It is used in nail polish, cosmetics, lubricants, floor carpets, tapestry, clothing treatments, rubber dentistry settings, as a fuel stabilizer, in leather varnishes and lacquers, as a concrete additive, as an adjusting agent for lead chromate paint pigments, lacquer manufacturing, and methyl methacrylate applications. DiBP is also used in printing inks for paper and packaging. Because DiBP has similar properties as dibutyl phthalate (DBP), it can be used as a substitute for DBP. [1]. DIBP is used as a plasticizer in a wide range of materials including polyvinyl chloride (PVC) formulations, as a softener, in viscosity adjustment, in clothing treatments, as a fuel stabilizer, as a concrete additive, etc. DIBP has also been classified by the Food and Drug Administration (FDA) as an indirect food additive through its use as a component of adhesives [2].

Children's Exposure: DIBP has been detected in crayons, bar ends of run bikes, erasers, school bags, selected toys and childcare products produced from foam plastic in Denmark and in dolls and figures in Germany [1]. DIBP has also been reported in house dust and in indoor air in Germany [1]. DIBP metabolites (MIBP) have been detected in human urine samples in the U.S. general population, and in Germany [2]. Urinary MIBP levels have increased over the past four surveys in all age groups, genders, and races, and in total. CHAP calculations estimate that the median/high (95th percentile) intake from NHANES biomonitoring data for DIBP is 0.17/1.0 μg/kg-day, respectively, in pregnant women [3].

Toxicity:

DIBP is found on the following authoritative lists:

- EU REACH Candidate List of Substances of Very High Concern for Authorization (SVHC list). Reason for listing: Toxic for Reproduction [4].
- EU – Annex VI CMRs: Reproductive Toxicity Category 1B [5].
- EU R-phrases: R61 May cause harm to the unborn child [5].
- EU R-phrases: R62 Possible risk of impaired fertility [5].
- EU GHS H-statements: H360Df May damage the unborn child. Suspected of damaging fertility [5].
- EU – REACH Annex XVII CMRs – Reproductive Toxicity Category 1B [5].
- EPA 2014 TSCA Work Plan list for meeting the criteria for Reproductive Toxicity [6].

Reproductive Toxicity: Several studies report reproductive toxicity for DIBP in animals. For example short-term oral exposure to DiBP caused significant adverse testicular effects in male adolescent rats including decreased testes weights, increased numbers of apoptotic spermatogenic cells, disorganized or reduced vimentin filaments in Sertoli cells, elevated testicular testosterone levels, decreased testicular zinc levels, and marked inhibition of spermatogenesis and desquamation of spermatocytes with effects seen at doses as low as 500 mg/kg-day. Similar findings were reported in rats treated with MIBP (DIBP metabolite). A similar study in mice found a significant decrease in testes weight at 1,000 mg/kg-day [1]. Subchronic oral exposure to DiBP resulted in marked significant reductions in absolute and relative testes weights of adult male rats fed 5% in the diet for 4 months in another study[1].

Developmental Toxicity: One study found postnatal effects of in utero exposure to DiBP on male reproductive development. DiBP was administered via gavage to pregnant Sprague-Dawley rats at 0, 125, 250, 500, or 625 mg/kg-day on gestation days 12–21. Effects observed in male offspring included

reduced anogenital distance, decreased pup weight, delayed separation of the prepuce from the glans penis, increased thoracic areolas and/or nipples, decreased testes and epididymis weights, increased incidence of testicular tubular degeneration-atrophy/hypoplasia, and increased incidence of external malformations, including hypospadias, exposed os penis, nonscrotal testes, and azospermia. 250 mg/kgday was identified as the LOAEL. The NOAEL was 125 mg/kg-day[1]. Other studies of pregnant rats exposed orally to DIBP during gestation have reported that DiBP exposure in utero results in significant adverse effects to the offspring of the exposed dams. For example in one study DiBP was administered via gavage to pregnant Sprague-Dawley rats resulting in significantly more resorptions at ≥500 mg/kg-day and significantly fewer live fetuses per litter and lower fetal body weight at ≥750 mg/kg-day. Internal examination revealed undescended testes in 56 and 70% of the male fetuses at 750 and 1,000 mg/kg-day, respectively. These results indicate developmental NOAEL and LOAEL values of 250 and 500 mg/kg-day, respectively [1]. In another study researchers exposed pregnant Sprague-Dawley rats to DiBP via gavage resulting in a marked increase in resorptions, a significant reduction in the number of live fetuses per litter, and a significant decrease in fetal body weight at ≥500 mg/kg-day and greater incidences of external, visceral, and skeletal malformations at ≥750 mg/kg-day [1]. Several epidemiologic studies measured urinary concentrations of MIBP (a DIDP metabolite). Of those that did, there were associations of maternal urinary MIBP concentrations with measures of male reproductive tract development (specifically, shortened anogenital distance [3]. And in humans several studies reported associations of MBP with poorer scores on neurodevelopment tests [3].

Additional Considerations: The Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives (CHAP) recommended to the U.S. Product Safety Commission in July, 2014 that DIBP should be permanently banned from use in children's toys and child care articles at levels greater than 0.1 % [3].

1. United States Consumer Product Safety Commission (CPSC), 2010. Memorandum: Toxicity Review of Diisobutyl phthalate (DiBP).
2. EPA, 2014. Preliminary Materials for the Integrated Risk Information System (IRIS): Toxicological Review of Diisobutyl Phthalate (CASRN No. 84-69-5).
3. Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives (CHAP), July, 2014. Report to the U.S. Consumer Product Safety Commission Directorate for Health Services.
4. ECHA Candidate List of substances of very high concern for Authorisation (SVHC), http://echa.europa.eu/candidate-list-table
5. ECHA Substance Information, Dipentyl phthalate CAS # 131-18-0, Summary of Classification and Labelling, https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/14308, retrieved 10/11/16.
6. U.S. Environmental Protection Agency, 2014. TSCA Work Plan for Chemical Assessments: 2014 Update. https://www.epa.gov/sites/production/files/2015-01/documents/tsca_work_plan_chemicals_2014_update-final.pdf

Diisooctyl phthalate (DIOP) (CAS # 27554-26-3)

Uses: Plasticizer for vinyl, cellulosic and acrylate resins, and synthetic rubber, additive in plastics that will come into contact with food [1].

Exposure: In one study the use of DIOP has been reported in teethers (10.2%) and pacifiers (17.1%). In the U.S., they are also reported in shower mats. The FDA has approved DIOP for use in adhesives or surface resin and polymer coatings for products that have contact with food (products intended to be used in production, manufacturing, packing, transport, or holding of food) [2].

Reproductive and Developmental Toxicity: Female CD-1 mice were exposed to 0, 44, 91, 190.6, or 292.5 mg/kg bw DIOP in their diet during gestation. The number and percent of resorptions, late fetal deaths, and dead and malformed fetuses were all increased in response to 190.6 and 292.5 mg/kg bw treatments. Female fetal weight and the number of live fetuses per litter for both sexes were significantly reduced at 190.6 and 292.5 mg/kg bw doses. A significant increase in both the percentage of fetuses with external, visceral, and skeletal malformations and the percentage of malformed fetuses per litter were observed with dosing as low as 91 mg/kg bw [1]. In a two-generation study, male/female Swiss CD-1 mice were exposed daily to 0, 14, 140, or 420 mg/kg of DIOP in their diet throughout a cohabitation period. When the F1 litters were sexually mature, they were mated with animals from different litters within the same group. At necropsy the F1 animals showed a significant decrease in the number of litters/pair, live pups/litter, mean live pup weight and proportion of live pups at 140 mg/kg/day. Exposure to 420 mg/kg/day resulted in significant infertility during the continuous breeding phase of the study which was seen in both sexes. Exposure to the high dose in the crossover study also resulted in male specific effects including reduced testis, epididymis, prostate weights, percentages of motile sperm and abnormal sperm, and sperm concentration in the males. In females effects included reduced combined weight of ovaries, oviducts and uterus. Both sexes exhibited increased liver weights. The majority of high-dose male mice evidenced some degree of bilateral atrophy of the seminiferous tubules[1].

Additional Considerations: The Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives (CHAP) recommended to the U.S. Product Safety Commission in July, 2014 that DIOP should be subject to an interim ban from use in children's toys and child care articles at levels greater than 0.1 % [3].

1. Toxnet Hazardous Substances Data Bank (HSDB). Diisooctyl Phthate RN: 27554-26-3. http://toxnet.nlm.nih.gov. Retrieved 7/11/16.
2. United States Consumer Product Safety Commission (CPSC), 2010. Memorandum: Toxicity Review of Diisodecyl phthalate (DIOP).
3. Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives (CHAP), July, 2014. Report to the U.S. Consumer Product Safety Commission Directorate for Health Services.