BASF Corporation

Attached are our comments submitted to Canada (ECCC/HC) last year in response to their request for information on uses and alternatives to DEHP. Given that it prepared a year ago, a few revisions are needed; however, the document provides a good overview of important applications.

BASF

We create chemistry

February 2, 2021

Via Electronic Mail

Environment and Climate Change Canada
Chemicals Management Division
Gatineau Quebec K1A 0H3

Email: eccc.substances.eccc@canada.ca

Comments on ECCC/HC Risk Management Approach for DEHP (December 2020)

To whom it may concern:

BASF Corporation[1] is pleased to submit these comments to Environment Canada and Climate Change and Health Canada in response to the proposed Risk Management Approach for 1,2-benzene-dicarboxylic acid, bis(2-ethylhexyl) ester (di-2-ethylhexyl phthalate, DEHP).[2] We appreciate the opportunity to provide public comments on this proposal.

We particularly would like to address available alternatives to DEHP and how they might be used in the applications listed in the following table from the ECCC/HC document:

Activity	Information needs
Import, use, sale, and/or offer for sale of DEHP or a product containing it for use in applications including: • plastic products such as plastic materials; • medical devices; • floor coverings; • building construction materials; • electrical and electronic products; • wire and cable; and • food packaging materials	• Description of the specific use of DEHP in your activity, including its quantity and concentration. • Known alternatives to DEHP suitable to the specific use/function. • Achievable timeline for your company to complete a phase out of DEHP, explaining significant challenges, cost estimates and efficiency or suitability of alternatives.

The following table summarizes the likely alternatives for these applications; details are presented in the following sections of these comments. The ECCC/HC proposal references older assessments of alternative plasticizers; e.g., Massachusetts TURI in 2006 and US Consumer Product Commission (CPSC) in 2014. Our comments will be based in part on numerous new or updated reviews over the past few years, including new risk assessments on phthalate substitutes by CPSC. The appendix also includes a list of acronyms for the various plasticizers discussed in this document.

[1] BASF Corporation is a subsidiary of BASF SE and is a manufacturer of plasticizers including some ortho-phthalates as well as di-2-ethylhexyl terephthalate, Hexamoll® DINCH, adipates, trimellitates, and polymeric plasticizers.

[2] ECCC and HC. Risk Management Approach for 1,2-benzene-dicarboxylic acid, bis(2-ethylhexyl) ester, CAS RN 117-81-7, December 2020.

BASF Corporation
11750 Katy Freeway
Suite 120
Houston, TX 77079

Activity	Alternatives to DEHP
Plastic materials	For general purpose uses: all products listed below, depending on the application.
Medical devices	DINCH, DOTP, TOTM, DEHA, ATBC, BTHC
Floor coverings	DOTP, DINCH, dibenzoates, biobased plasticizers
Building construction	DINP, DPHP, DIDP, linear ortho-phthalates
Electronics	See wire and cable
Wire and cable	DINP, DPHP, DIDP, linear ortho-phthalates, TOTM and other trimellitates
Food packaging	DINCH, DOTP, DEHA, ATBC, ESBO, and others

1. Plastic products such as plastic materials

This is category is not specific. DEHP may or may not be used in various applications depending on the performance requirements. The comments below for more specific uses are helpful examples.

For products manufactured in the U.S. and Canada, DEHP has been largely replaced by higher molecular weight ortho-phthalates such as diisononyl phthalate (DINP) or by alternative plasticizers such as di-2-ethylhexyl terephthalate (DOTP). Imported products, particularly from Asia very often are plasticized with DEHP since it is still the primary plasticizer produced in that region.[3]

2. Medical devices

The most important current use of DEHP is in medical devices ranging from tubing, IV infusion bags, and blood product containers, to a variety of miscellaneous products. Device makers can provide the best input on the challenges, such as timelines and costs for development and testing, to change to other plasticizers or to other materials. The following comments highlight important reviews, studies, and regulatory developments with respect to alternative plasticizers for this market.

Europe

Most of the regulatory activity around plasticizers in medical devices is taking place in Europe. DEHP is classified under CLP (Reg (EC) No 1272/2008 , the European Implementation of the Globally Harmonized System (GHS), as Category 1B for reproductive and developmental effects, and subsequently, is a substance of very high concern (SVHC) for these endpoints as well as for endocrine disruption in humans; SVHC classification for endocrine disruption for the environment is proposed. It was also subject to Authorisation for specific uses. Medical devices

[3] DEHP consumption in China was 47% of the total plasticizer demand in 2017 compared to 12% or less in the U.S. China also consumes over 40% of the global demand for plasticizers compared to around 13% for the North America. See Malveda, M., et al., *Plasticizers*, Chemical Economics Handbook, IHS Markit, 2018.

have up to now been excluded from the REACH actions since their uses are regulated through other regulations (Reg (EU) 2017/745 (MDR) and Reg (EU) 2017/746); however, the endocrine disruption for the environment may have a more significant effect because this is not part of the normal risk evaluation of medical devices. More importantly, the new medical device regulation (MDR) includes a 0.1% concentration limit for materials “classified as category 1A and 1B carcinogenic, mutagenic, and reprotoxic (CMR) substances and endocrine disrupting chemicals (EDCs) in devices that are invasive and come into direct contact with the body, or (re)administer, transport or store medicines, body liquids or other substances, to and from the body. Devices will be allowed to contain substances above the 0.1% concentration limit if justification is provided.” As noted above DEHP is classified as CMR and EDC, and its use has to be justified following the Guidance as published by the Scientific Committee Health, Environmental and Emerging Risks (SCHEER).[4] Owing to COVID-19, the effective date has been extended to May 2021.

The European Commission's Scientific Committee on Emerging and Newly Identified Health Risks (SCENIR) revised its opinion on DEHP exposure from medical equipment and its review of potential alternatives in 2016.[5]

The European Pharmacopoeia (9th Edition) from EDQM (European Directorate for the Quality of Medicines) lists, in addition to DEHP, four additional plasticizers for containers for human blood and blood components, tubing used in sets for the transfusion of blood and blood components, empty sterile containers of plasticized PVC for human blood and blood components, and sterile containers of plasticized PVC for human blood containing anticoagulant solution. The new plasticizers are:[6]

Additive 24: DINCH (cyclohexane 1,2-dicarboxylic acid, diisononyl ester)
[= Hexamoll® DINCH, the EU Pharmacopeia does not list brand names]
Additive 25: BTHC (butyryl tri-n-hexyl citrate)
Additive 26: TOTM (tris(2-ethylhexyl) trimellitate)
Additive 27: DEHT (bis(2-ethylhexyl) terephthalate)

Blood products

DEHP has some unique performance properties when used in PVC storage containers for blood products, particularly for whole blood / red blood cell storage. Trace amounts of the plasticizer that migrate into the blood help stabilize the red blood cells and reduce the amount of hemolysis. A citrate plasticizer, BTHC, was introduced over 25 years ago as a replacement for

[4] SCHEER (Scientific Committee on Health, Environmental and Emerging Risks), Guidelines on the benefit-risk assessment of the presence of phthalates in certain medical devices covering phthalates which are carcinogenic, mutagenic, toxic to reproduction (CMR) or have endocrine-disrupting (ED) properties, final version adopted at SCHEER plenary on 18 June 2019

[5] Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), "Opinion on the Safety of Medical Devices Containing DEHP-Plasticized PVC or Other Plasticizers on Neonates and Other Group Possibly at Risk (2015 Update)," February 2016. [Online]. Available: https://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_047.pdf. [Accessed 29 April 2016].

[6] https://pvcmed.org/four-new-plasticisers-now-added-european-pharmacopoeia/.

DEHP but only saw limited use. Recently several studies with DINCH (i.e., Hexamoll® DINCH) suggest that it is a suitable replacement; one similar study has been carried out with DOTP.

Using the additive solution AS-5, storage bags with DINCH mixed weekly over the 6 weeks storage period can be used to achieve similar performance to DEHP (Dumont, et al. (2012).[7] However, mixing of the bags is not the usual practice in blood banks. Using CPD as the additive, Devine, et al. (2013)[8] showed that RBC stored in DINCH bags did not differ in hemolysis from RBC stored in DEHP bags. A study by the Canadian Blood Center also showed similar hemolysis rates for DEHP and DINCH when the bags were mixed.[9] With newer additive solutions such as AS-7 (SOLX®), E-Sol5,[13] and PAGGS-M, the performance with DINCH is the same as with DEHP.[10] Dabay[11] compared the hemolysis rate in standard DEHP bags to DINCH bags with AS-7/SOLX®. Promising results also were seen with DOTP and PAGGS-M.[12]

The following table summarizes the results:

Effect of Plasticizer Type on Red Blood Cell (RBC) Stability				
Reference	**Plasticizer**	**Preservative**	**Blood product**	**Hemolysis, %**
Dumont, et al., (2012)	DEHP	AS-5	RBC	0.37
	DINCH (mixed)	AS-5		0.32 – 0.36
	DINCH (unmixed)	AS-5		0.56
	DEHP	AS-1		0.37
	DINCH (unmixed)	AS-1		0.52
Dabay, et al., (2012)	DEHP	AS-1	RBC	0.35
	DINCH	AS-7 (SOLX®)		0.36
Radwanski, et al. (2013)[13]	DEHP	AS-1	RBC	0.27
	DINCH	PAGGS-M		0.31
	DINCH	E-Sol 5		0.16

[7] Dumont LJ, Baker S, Dumont D, et al. 2012. Exploratory in vitro study of red blood cell storage containers formulated with an alternative plasticizer. *Transfusion* **5**, 1439-45.

[8] Devine D., et al. 2013. *Vox Sanguinis* 105, Suppl. 1, 27/28.

[9] Bicalho B, Serrano K, dos Santos Pereira A, et al. 2016. Blood bag plasticizers influence red blood cell vesiculation rate without altering the lipid composition of the vesicles. *Transfus Med Hemother* **43**,19-26.

[10] Lagerberg, JW, 2012, Transfusion 52 Suppl, SP50, p.73A; Lagerberg JW, Gouwerok E, Vlaar R, et al. 2015. In vitro evaluation of the quality of blood products collected and stored in systems completely free of di(2-ethyl hexyl) phthalate plasticized materials. Transfusion 55, 522-31. Also see Footnote 16.

[11] Dabay, M, Kline, L, Zia, M, Kandler, R. 2012. Evaluation of SOLX® Red Blood Cells Stored in DINCH Plasticized PVC Container. *Transfusion*, 52, Suppl. SP56.

[12] Graminske S, Puca K, Schmidt A, et al. In vitro evaluation of di(2-ethylhexyl) terephthalate plasticized polyvinyl chloride blood bags for red blood cell storage in AS-1 and PAGGSM additive solutions. 2018. *Transfusion* 58, 1100 - 1107.

[13] Radwanski, K, Min, K, 2013. Red Blood Cell (RBC) Storage in DINCH-PVC Storage Containers using Current and Next Generation Additive Solutions, Transfusion, 53, Suppl. 51A S83-040A

Devine, et al. (2013)	DEHP	CPD	RBC	0.39
	DINCH	CPD		0.42
	BTHC	CPD		0.85
Lagerberg, et al. (2012)	DEHP	PAGGS-M	RBC	0.15
	DINCH	PAGGS-M		0.20
	BTHC	PAGGS-M		0.45
Lagerberg, et al. (2015)	DEHP	SAG-M	RBC	0.23
	DINCH	SAG-M		0.57
	DINCH	PAGGS-M		0.24
	DINCH	PAGGS-M		0.19
Bicalho, et al. (2016)	DEHP	SAG-M	RBC	0.38
[bags were mixed weekly]	DINCH	SAG-M		0.40
	BTHC	SAG-M		0.86
Graminske, et al. (2018)	DEHP	AS-1	RBC	0.32
	DOTP	AS-1		0.49
	DOTP	PAGGS-M		0.38

Commercial storage bags include a preservative solution (additive solution). With the solutions historically used, DINCH and DOTP showed approximately 50% higher hemolysis than with DEHP in most studies. Given the known challenges with meeting US FDA clinical trial requirements, experts believe any alternative must offer the same or better performance than with DEHP.[14] Based on multiple studies with the newer preservatives, it appears that DINCH is a viable alternative to DEHP.

DINCH also may be used for platelet storage and has been used since 2013 by the Dutch blood bank Sanquin for pediatric platelet storage. In addition, Nair, et al. (2014)[15] and Lagerberg, et al. (2015)[16] also showed that DINCH may be used for plasma storage.

3. Flooring Coverings

BASF understands that, as a result of market demand and purchasing policies that specify flooring without ortho-phthalates such as DEHP or DINP, manufacturers of vinyl flooring have largely moved away from the use of the ortho-phthalates to alternatives.[17] One of the most important and widely used alternatives in North America for flooring and other applications is bis(2-ethylhexyl) terephthalate (CAS 6422-86-2; DOTP or DEHT). A commercial example is BASF's Palatinol® DOTP. DOTP performs well in flooring applications, is well-studied, and has

[14] Dumont, LJ and AuBuchon, JP. 2008. Evaluation of proposed FDA criteria for the evaluation of radiolabeled red cell recovery trials. *Transfusion*, **48**, 1053-1060.

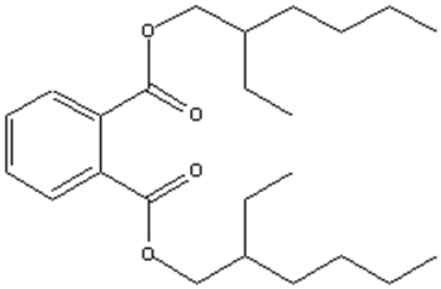
[15] Nair, BCS, VIDYA, R, ASHALATHA, PM, 2014. Studies on the storage of pooled platelets in non DOP PVC containers. Int J Pharm Bio Sci 2014 Jan; 5(1): (P) 520 - 531

[16] Lagerberg JW, Gouwerok E, Vlaar R, et al. 2015. In vitro evaluation of the quality of blood products collected and stored in systems completely free of di(2-ethyl hexyl) phthalate plasticized materials. Transfusion 55, 522-31.

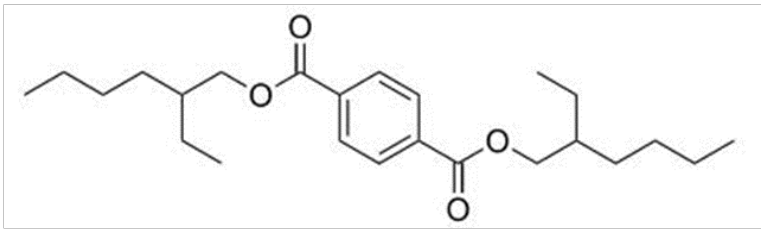
[17] https://www.floordaily.net/floorfocus/the-greening-of-lvt-mannington-armstrong-tarket; and https://www.constructionspecifier.com/walk-this-way-new-trends-in-vinyl-flooring/.

a demonstrated low hazard profile; these are all essential criteria for a valid alternatives assessment.[18]

Terephthalates are different structurally from ortho-phthalates since the two ester groups are in the 1,4 position versus the 1,2 position. This can be seen in the following example comparing DOTP and di-2-ethylhexyl phthalate (DEHP).



DEHP (ortho-phthalate)



DOTP (tere-phthalate)

This structural difference results in a minimal impact on the performance of DOTP compared to DEHP; however, its toxicological behavior is significantly different. DEHP is currently classified in Europe and in California (OEHHA) for reproductive and developmental concerns;[19] DOTP is not classified and has a demonstrated low hazard profile as discussed in the following section.

Low Hazard Profile for DOTP

DOTP has a full toxicological profile and no relevant hazards. It has been reviewed by the European Food Safety Authority (EFSA),[20] ANSES under the EU Regulatory Management Option Analysis (RMOA) process,[21] NSF International,[22] and more recently by the U.S. Consumer Product Safety Commission (CPSC).[23]

---

[18] For example: https://dtsc.ca.gov/scp/alternatives-analysis/.

[19] It should be noted that the reproductive and developmental effects depend upon the alcohol chain length and not all ortho-phthalates show the same adverse effects. See Fabjan, E.; Hulzebos, E.; Mennes, W.; Piersma, A. W. "A Category Approach for Reproductive Effects of Phthalates," *Crit. Rev. Tox.*, **2006**, *36*, 695-726.

[20] European Food Safety Authority (EFSA), "Opinion of the Scientific Panel on Food Additives, Flavorings, Processing Aids and Materials in Contact with Food (SFC). The EFSA Journal 628-633:1-19," 2008.

[21] ANSES, "Risk Management Options Analysis (RMOA) - Diethylhexyl Terephthalate," January 2016. [Online]. Available: https://www.echa.europa.eu/documents/10162/dd0220b0-1187-4c2b-8991-51ddbbc9d462. [Accessed 18 May 2016].

[22] Ball, G. L.; McLellan, C. J.; Bhat, V. S. "Toxicological Review and Oral Risk Assessment of Terephthalic Acid and Its Esters: a Category Approach," *Crit. Rev. Tox.*, 2012, 42, 28-67. DOI: 10.3109/10408444.2011.623149.

[23] Updated risk assessment for a number of alternative plasticizers are now available on the CPSC website, including one for DOTP: https://www.cpsc.gov/s3fs-public/Toxicity%20Review%20of%20DEHT.pdf?FObpuBBqgypVtw7gIEGMFXHN5H7vbeEz.

DOTP has been assessed using the GreenScreen® methodology based on hazard classifications for 18 human health, environmental, and physical hazard endpoints.[24] It received a Benchmark score of 3_{DG} in an assessment in 2012[25] and an updated assessment in 2016/17.[26] This means that the product was classified as a low hazard for all endpoints and met the criteria for Benchmark 4 (the highest), except for one or more allowed data-gaps. In the most recent assessment, the only identified data gap was for endocrine activity. As noted in Harmon and Otter (2018), BASF has concluded there is no data gap for this end point based on in vitro data and in vivo data from various chronic and subchronic studies.[27] It is important to note that DOTP clearly shows no evidence of adverse endocrine effects based on the following data:

- No anti-androgenic effects similar to those observed with some ortho-phthalates[28]
- No estrogenic effects in vitro or in vivo[29]
- Inactive in a number of US EPA ToxCast and EDSP21 assays[30]
- No suggestion of thyroid or adrenal gland effects from sub-chronic and chronic studies[31]

In addition, ANSES under the EU RMOA process determined that there was "no alert . . . on potential endocrine disruption properties of the substance" and concluded there were no risk management measures necessary.[32]

The two commercial U.S. made products also are listed in the CleanGredients® database, which is based on the US EPA Safer Choice criteria.

---

[24] For more details see, http://www.greenscreenchemicals.org/.

[25] ToxServices, "Di(2-ethylhexyl) Terephthalate (DEHT) (CAS #6422-86-2)," 11 October 2012. [Online]. Available: http://www.greenchemistryandcommerce.org/documents/DEHTVERIFIEDASSESSMENT_final.pdf. [Accessed 11 September 2017].

[26] NSF International, "GreenScreen Assessment for Bis(2-ethylhexyl) terephthalate (6422-86-2)," 2017. The assessment is currently not publicly available but can be provided to Washington DOE upon request.

[27] Harmon, J. P. and Otter, R. "Green Chemistry and the Search for New Plasticizers," *ACS Sustainable Chem. Eng.* **2018**, 6, 2078 – 2085.

[28] Gray, Jr., L. E.; Ostby, J.; Furr, J.; Price, M.; Veeramachaneni, D. N.; Parks, L. "Perinatal Exposure to the Phthalates DEHP, BBP, and DINP, but Not DEP, DMP, or DOTP, Alters Sexual Differentiation of the Male Rat," *Toxicol. Sci.*, **2000**, *58*, 350-365; and Furr, J. R.; Lambright, C. S.; Wilson, V. S.; Foster, P. M.; Gray, Jr., L. E. "A Short-Term In Vivo Screen Using Fetal Testosterone Product, a Key Event in the Phthalate Adverse Outcome Pathway, to Predict Disruption of Sexual Differentiation," *Toxicol. Sci.*, **2014**, *140*, 403-424.

[29] Ball, G. L.; McLellan, C. J.; Bhat, V. S. "Toxicological Review and Oral Risk Assessment of Terephthalic Acid and Its Esters: a Category Approach," *Crit. Rev. Tox.*, **2012**, *42*, 28-67.

[30] US EPA, "Endocrine Disruptor Screening Program (EDSP) Estrogen Receptor Bioactivity," 2015. [Online]. Available: https://www.epa.gov/endocrine-disruption/endocrine-disruptor-screening-program-edsp-estrogen-recpetor-bioactivy. [Accessed 20 June 2016]; and US EPA, "EDSP21 Dashboard," [Online]. Available: https://actor.epa.gov/edsp21/. [Accessed 11 September 2017].

[31] See reference in Footnote 22.

[32] ANSES, "Risk Management Options Analysis (RMOA) - Diethylhexyl Terephthalate," January 2016. [Online]. Available: https://www.echa.europa.eu/documents/10162/dd0220b0-1187-4c2b-8991-51ddbbc9d462. [Accessed 18 May 2016].

Diisononyl cyclohexanedicarboxylate (DINCH) in Vinyl Flooring

Another important alternative plasticizer is DINCH (e.g., BASF's Hexamoll® DINCH). It is used in applications with close human contact such as toys, medical devices, and food contact. It also is an important ortho-phthalate alternative for use in floor coverings, especially in Europe.

Government agency assessments of DINCH include a recent update by the US Consumer Product Safety Commission (CPSC),[33] the European Food Safety Authority (EFSA),[34] the Australian NICNAS,[35] the EU Scientific Committee for Emerging and Newly Identified Health Risks (SCENIHR),[36] and the French agency ANSES under the REACH Risk Management Options Analysis (RMOA).[37]

DINCH was assessed by NSF International for their drinking water standard.[38] It was assigned an overall score of Benchmark 2 using the GreenScreen® methodology[39] and is on the TCO Certified Accepted Substance List (ASL) that lists substances based on a score of GreenScreen® Benchmark 2 or higher.[40] In a report for the Washington Department of Ecology, Northwest Green Chemistry looked at several alternatives to certain ortho-phthalates; DINCH and DOTP were the only two plasticizers with sufficient data and external assessments to meet their criteria for Category A ("Category A alternatives have publicly accessible, full chemical

---

33 https://www.cpsc.gov/s3fs-public/Toxicity%20Review%20of%20DINX.pdf?n_tDo9yqCvnxEdDVuINE7tQba9lrg_XQ.

34 European Food Safety Authority (EFSA), "Opinion of the Scientific Panel on Food Additives, Flavorings, Processing Aids and Materials in Contact with Food (SFC). The EFSA Journal 395 to 401:1-221," 2006. [Online]. Available: http://echa.europa.eu/documents/10162/13632/information_requirements_r7a_en.pdf. [Accessed 20 June 2016].

35 National Industrial Chemicals Notification and Assessment Scheme (NICNAS), "Public Report: 1,2-Cyclohexanedicarboxylic Acid, 1,2-Diisononyl Ester ("Hexamoll DINCH"), File No: EX/170 (STD/1259)," 2012. [Online]. Available: https://www.nicnas.gov.au/__data/assets/word_doc/0003/6699/EX170FR.docx. [Accessed 21 June 2016].

36 Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), "Opinion on the Safety of Medical Devices Containing DEHP-Plasticized PVC or Other Plasticizers on Neonates and Other Group Possibly at Risk (2015 Update)," February 2016. [Online]. Available: https://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_047.pdf. [Accessed 29 April 2016].

37 ANSES, "Analysis of the Most Appropriate Risk Management Option (RMOA) - 1,2 Cyclohexanedicarboxylic Acid, Diisononyl Ester (DINCH)," January 2016. [Online]. Available: https://www.echa.europa.eu/documents/10162/fc77bffd-e7ec-4846-b080-11de2564e582. [Accessed 21 March 2016].

38 Bhat, V. S.; Durham, J. L.; Ball, G. L.; English, J. C. "Derivation of An Oral Reference Dose (RfD) for the Non-Phthalate Alternative Plasticizer 1,2-Cyclohexane Dicarboxylic Aicd, Di-Isononyl Ester (DINCH)," *J. Toxicol. Environ. Health B: Crit. Rev.*, **2014**, *17*, 63-94. http://dx.doi.org/10.1080/10937404.2013.876288.

39 ToxServices LLC, Diisononyl Cyclohexanedicarboxylate (DINCH) (CAS #474919-59-0, 166412-78-8), GreenScreen® for Safer Chemicals Assessment, May 17, 2017 [as of December 5, 2017, the report was no longer available for purchase from techstreet.com. The 2017 reports is an update to an assessment from 2013 that is available at http://www.greenchemistryandcommerce.org/projects/greenscreen-assessment-hexamoll-dinch. The assessment by NSF International is available upon request: NSF International, "GreenScreen Assessment for Hexamoll DINCH (Diisononyl Cyclohexanedicarboxylate) (CAS #166412-78-8, 47919-59-0) [Unpublished]," 2017.

40 https://tcocertified.com/accepted-substance-list/.

hazard assessment reports, and meet minimum hazard criteria.").[41] More recently, a new non-profit initiative ChemFORWARD created a database of alternative plasticizers based on assessments by two different profilers (i.e., primary assessment was verified by a second profiler) using Globally Harmonized System (GHS) and Cradle to Cradle criteria – DINCH is included as an example of safer chemistry.[42]

DINCH surprisingly was assigned a classification of moderate (with low confidence) for endocrine activity in the GreenScreen® assessments, which resulted in an overall score of Benchmark 2. One licensed profiler classified it as a low hazard (with low confidence), while another classified it as moderate based on thyroid effects observed in chronic and sub-chronic rodent studies.[38] In the assessments by NICNAS (Australia), the European Food Safety Authority (EFSA), and NSF International, specific studies have shown that the thyroid effects are caused by an indirect mechanism and are not relevant to humans. Furthermore, the French ANSES concluded through the Risk Management Options Analysis (RMOA) process that specifically focused on endocrine disruption, that no risk management measures were required.

As also noted in Harmon and Otter (2018),[43] DINCH was found to be negative in an EPA screen for fetal testosterone effects.[44] This work was done to identify possible anti-androgenic effects observed with some ortho-phthalates. DINCH also was negative for estrogen receptor bioactivity based on the ToxCast™ Endocrine Receptor Model[45] and the various EDSP21 assays.[46] These data and the weight-of-evidence from chronic and sub-chronic studies demonstrate that DINCH is not a concern for adverse endocrine effects. Regulatory and other assessments support this conclusion.

Hexamoll® DINCH and Palatinol® DOTP are "Accelerators" using BASF's Sustainable Solution Methodology® based on their significant contributions to sustainability in the area of Health and Safety.[47]

Alternatives Assessment – Avoid Regrettable Substitution

As discussed in Lavoie, et al. (2010), "substitution that is not informed by the best available information and science can lead to unintentional and undesired consequences," or what some

---

41 https://www.northwestgreenchemistry.org/news/alternatives-to-five-phthalates-of-concern-to-puget-sound-1.

42 https://www.chemforward.org/. Also see https://www.greenbiz.com/article/why-google-basf-and-sephora-are-coming-together-safer-chemistry.

43 Harmon, J. P. and Otter, R. "Green Chemistry and the Search for New Plasticizers," *ACS Sustainable Chem. Eng.* **2018**, *6*, 2078 – 2085.

44 Furr, J. R.; Lambright, C. S.; Wilson, V. S.; Foster, P. M.; Gray, Jr., L. E. "A Short-Term In Vivo Screen Using Fetal Testosterone Product, a Key Event in the Phthalate Adverse Outcome Pathway, to Predict Disruption of Sexual Differentiation," *Toxicol. Sci.*, **2014**, *140*, 403-424. https://doi.org/10.1093/toxsci/kfu081.

45 US EPA, "Endocrine Disruptor Screening Program (EDSP) Estrogen Receptor Bioactivity," 2015. [Online]. Available: https://www.epa.gov/endocrine-disruption/endocrine-disruptor-screening-program-edsp-estrogen-recpetor-bioactivy. [Accessed 20 June 2016].

46 US EPA, "EDSP21 Dashboard," [Online]. Available: https://actor.epa.gov/edsp21/. [Accessed 11 September 2017].

47 https://www.basf.com/us/en/who-we-are/sustainability/we-drive-sustainable-solutions/sustainable-solution-steering.html.

have called "regrettable substitution".[48] The choice of DOTP and DINCH as a plasticizers by vinyl flooring manufacturers is a good example of responsible and science-based alternative selection. The positive assessments and regulatory approvals for DOTP and DINCH described above support the goal of avoiding "regrettable substitution" and their broad use as an alternative to general purpose ortho-phthalates.

4. Building and Construction

DEHP likely had some limited use in building and construction applications but has been replaced by U.S. and Canadian formulators with other ortho-phthalates and alternative plasticizers. In some cases, DEHP does not meet and performance requirements and was not used. For example, roofing membranes are an important market for plasticized vinyl. Owing to the need for low temperature flexibility and superior outdoor weather performance, specialty linear ortho-phthalates as well as DINP and DPHP are used. The following table shows some applications and the plasticizers typically used:[49]

Use	Plasticizers
Water stop	DOTP, DINP
Caulks and sealants	Dibenzoates, DINP, DOTP, DINCH, DIDP
Pond and pool liners	DINP, DPHP, DIDP
Roofing membrane	DINP, DPHP, linear ortho-phthalates

5. Electrical and Electronic Equipment / Wire and Cable

The predominant use of plasticizers in these two categories is in PVC jacketing and insulation for the wire and cable market. As noted in Godwin and Krauskopf (2008),[50] general purpose plasticizers such as DEHP may be used to meet 60 °C UL-rated PVC formulations; however, DEHP is not widely used for these applications in North America. As discussed in Godwin and Krauskopf, "flexible PVC products rated for 75 – 80 °C performance require less-volatile plasticizers such as DINP, DIDP, DPHP, or 711P types. Performance ratings for even higher temperatures (i.e., 90 and 105 °C) require the low volatility higher-molecular-weight phthalates and / or trimellitates. In all cases, the optimum plasticizer choice is a function of wall thickness and other factors influencing oven aging . . ." The following table, which was adapted from Godwin and Krauskopf, shows examples of plasticizers that meet various oven aging tests and the corresponding UL temperature ratings.

---

[48] Lavoie, E. T.; Heine, L. G.; Holder, H.; Rossi, M. S.; Lee, II, R.E.; Connor, E. A.; Vrabel, M. A.; Difiore, D. M.; Davies, C. L. "Chemical Alternatives Assessment: Enabling Substitution to Safer Chemicals," *Environ. Sci. Tech.*, **2010**, *44*, 9244-9249.

[49] See Footnote 3 and Godwin and Krauskopf, "Monomeric Plasticizers" in *Handbook of Vinyl Formulating*, 2nd ed., Grossman, R. F., Ed., Wiley: New Jersey, 2008.

[50] See Goodwin and Krauskopf in Footnote 46.

Wall thickness (mil)	Test temperatures for 7-day aging, deg C			
	100 UL 60	113 UL 80, SAE-80	121 UL 90	136 UL 105
8	DIDP, DPHP	DUP	DUP	TOTM, TINTM
15	DIDP, DPHP	911P, DUP	DUP, DIDP/DTDP	DUP/TOTM
30	DINP, DOTP, DIDP, DPHP	DIDP	DIDP	DTDP/TINTM
60	DINP, DOTP, DIDP, DPHP	DIDP, DPHP	DIDP, DPHP	DUP, DTDP

6. Food Packaging

A recent publication by FDA scientists (Carlos, et al., 2018) reported on plasticizers found in food contact applications in North America; it is likely not exhaustive, but is, to our knowledge, representative and useful.[51]

In addition to the ortho-phthalates DEHP, DINP, and DIDP, several other plasticizers were found in the FDA testing, including acetyl tributyl citrate (ATBC), di-2-ethylhexyl adipate (DEHA or DOA), diisononyl adipate (DINA), epoxidized soybean oil (ESBO), di-2-ethylhexyl terephthalate (DEHT or DOTP), and diisononyl cyclohexane-1,2-dicarboxylate (DINCH). The following table summarizes the regulatory status and commercial availability of these products.

[51] Carlos, de Jager, and Begley, "Investigation of the primary plasticizers present in polyvinyl chloride (PVC) products currently authorized as food contact materials," *Food Add. Contam.: Part A,* 2018, 35, 1214 – 1222.

Non-ortho-phthalate plasticizers reported in Carlos, et al. 2018.

Plasticizer	FDA	EU EFSA	Availability (US, Canada) [1]	Comments[2]
ATBC CAS# 77-90-7	Prior sanctioned 21 CFR 181.27 21 CFR 175.105 21 CFR 175.300 21 CFR 176.170 21 CFR 176.180 21 CFR 177.1210 21 CFR 177.2600 21 CFR 178.3740	93760 SML = 60 mg/kg	Vertellus	Tubing and cap gaskets.
DEHA CAS# 103-23-1	21 CFR 175.105 21 CFR 177.1200 21 CFR 177.1210 21 CFR 177.2600 21 CFR 177.1400 21 CFR 178.3740	31920 SML = 18 mg/kg	BASF, Eastman, PolyOne, and imports	Food service and commerical wraps. Also used as a secondary plasticizer to improve low temperature performance.
DINA CAS# 33703-08-1	21 CFR 178.3740		BASF, ExxonMobil, PolyOne	Food service and commerical wraps. Also used as a secondary plasticizer to improve low temperature performance.
ESBO CAS# 8013-07-8	Prior sanctioned 21 CFR 181.27 21 CFR 172.723 21 CFR 175.105 21 CFR 175.300 21.CFR 177.1650 21 CFR 178.3910	88640 SML = 60 mg/kg (baby foods = 30 mg/kg)	Arkema, Galata Valtris	Cap gaskets for non-alcoholic bottled drinks and jarred foods.
DOTP CAS# 6422-86-2	FCN 1056 (Eastman, PVC) FCN 1473 (BASF, PVC) FCN 1778 (BASF nitrile rubber) 21 CFR 177.1210	92200 SML = 60 mg/kg	BASF, Eastman, and imports	Tubing and cap gaskets for bottled beer and jarred foods.
DINCH CAS# 474919-59-0, 166412-78-8	Health Canada approval in 2010.	45705 SML = 60 mg/kg	Imported (BASF and others)	Reported in one imported cap gasket for jarred foods.

[1] IHS Markit, Plasticizers, 2018.
[2] Uses as reported in Carlos, et al., 2018.
FCN Food contact notification
SML Specific migration limit; all additives limited to 60 mg/kg, but some substances have a lower SML.

These six plasticizers have been commercially available for a number of years and are well characterized with respect to health and safety:

A Acetyl tributyl citrate (ATBC) – The plasticizer has been used in applications such as toys and food contact materials for many years. The most recent assessment of the toxicology data is in a review commissioned by the U.S. Consumer Product Safety Commission (CPSC).[52] TCO Certified includes it in their Accepted Substance List (ASL) based on a GreenScreen® Benchmark score of 3.[53] We don't have access to the GreenScreen® assessment by ToxServices; however, this appears to be a reasonable Benchmark score based on our review of the available data (see table below). In Europe

[52] https://www.cpsc.gov/s3fs-public/Toxicity%20Review%20of%20ATBC.pdf?AsgeTCxYY0_3F.wMkaokmHmiD5LWh.zO.
[53] https://tcocertified.com/accepted-substance-list/

under EFSA regulations, it is only subject to the general specific migration limit (SML) of 60 mg/kg.

B Di-2-ethylhexyl adipate (DEHA or DOA) and diisononyl adipate (DINA) – DEHA, and to a lesser extent DINA, have been used for more than 20 years as plasticizers in vinyl commercial and food service film (typical consumer cling films are made with polypropylene). DEHA performs well in this application due to oxygen permeability of films plasticized with it.[54] Outside of this application, DEHA and DINA are not usually used as primary plasticizers but as secondary plasticizers in formulations to improve low temperature flexibility.[55] In this regard they are not replacements for ortho-phthalates such as DEHP and DINP but are specialty additives used to meet a particular technical requirement. In Europe, under EFSA regulations, DEHA is subject to a SML of 18 mg/kg.

DEHA and DINA have been reviewed in assessments commissioned by US CPSC.[56] They also are included in the TCO Certified ASL with GreenScreen® Benchmark scores of 2.[57] We do not have access to the full assessment but consider this to be a conservative conclusion. DEHA has an almost complete dataset that shows overall low hazard (see table below). We assume it was assigned a moderate cancer classification since it is an EPA Class C carcinogen; however, it is IARC Class 3 (not classifiable), and the observed tumors are attributed to peroxisome proliferation (likely not relevant to humans) and were seen in mice but not in rats or dogs.

C Di-2-ethylhexyl terephthalate (DOTP, DEHT) – DOTP is cleared by U.S. FDA for use in closures with sealing gaskets in food containers (21 CFR 177.1210), and through three Food Contact Notifications (FCN). The FCN's are manufacturer specific and are available from Eastman (No. 1056, vinyl repeat use applications) and BASF (1473, vinyl repeat use applications, and 1778, nitrile rubber repeat use applications).[58] In Europe, under EFSA regulations, it is only subject to the general specific migration limit (SML) of 60 mg/kg.

As described above in the comments on Floor Coverings, DOTP has a full toxicological profile and no relevant hazards (see the discussion above for more details).

D Diisononyl cyclohexane-1,2-dicarboxylate (DINCH) – DINCH (e.g., Hexamoll® DINCH from BASF) has broad global clearances for food contact applications outside the US (EFSA, Japan, China, Canada,[59] Australia). Beyond food contact uses, it is used globally for applications with close human contact, such as those involving toys, medical devices,

---

54 Sears, J. K. and Darby, J. R., *The Technology of Plasticizers* (John Wiley & Sons: New York), 1982, p. 443.
55 Grossman, R. F., ed., *Handbook of Vinyl Formulating*, 2nd Edition, Wiley Interscience, 2008.
56 https://www.cpsc.gov/s3fs-public/Toxicity%20Review%20of%20DEHA.pdf?TSiSSb20aUy68dV0qk1AllBUrIaPFSaE and https://www.cpsc.gov/s3fs-public/ToxicityReviewforDiisononylAdipate062019.pdf?vM1E2MpKwInTRd11A7yyAUAZq8gAn2Xl.
57 See Ref 53.
58 See FDA FCN database: https://www.fda.gov/food/packaging-food-contact-substances-fcs/inventory-effective-food-contact-substance-fcs-notifications,
59 Health Canada, Bureau of Chemical Safety, Hexamoll® DINCH, "No Objection Letter," 2010.

and indoor products. The BASF product has an extensive toxicological database and no relevant hazards (see discussion above under Floor Coverings for more details).

E Epoxidized soybean oil (ESBO) – ESBO is cleared under various 21 CFR sections and is listed as prior sanctioned. Many PVC formulations incorporate ESBO at around 2–5 parts per hundred parts of PVC resin. ESBO is used for plasticization and heat stabilization; this is due to the observed synergism with mixed-metal stabilizers that provides resistance to heat and sunlight.[60] In the Carlos, et al., 2018, study, it was found in several cap gaskets for jarred foods.

The toxicological profile shown in Table II indicates an overall low hazard concern. It also has been reviewed by EFSA[61] and US CPSC.[62] The TCO Certified ASL reports a Benchmark score of 3; however, we do not have access to the full assessment.

Hazard Summary Plasticizers in Food Contact

Endpoint	DOTP	ATBC	DEHA	DINA	ESBO	DINCH
Assessment by:	NSF	BASF	BASF	BASF	BASF	NSF
Data source	BASF	REACH dossier, SDS, CPSC				BASF
Cancer	L	L	M, EPA C, IARC 3	*Read across*	L	L
Mutagenicity	*L*	L	L	L	L	L
Reproductive	L	L	L	*Read across*	L	L
Developmental	L, rat and rabbit	No full pre-natal	L, rat and rabbit	*Read across*	L	L, rat and rabbit
Endocrine Activity	dg	dg	dg	dg	dg	M
Acute Toxicity	L	L	L	L	L	L
Systemic Toxicity	L	L	L	L	L	L
Neurotoxicity	L	dg	*L*	*L*	*L*	L
Skin Sensitization	L	L	L	*QSAR*	L	L
Respiratory Sensitization	*L*	*L*	*L*	*L*	*L*	*L*
Skin Irritation	L	L	L	L	M	M
Eye Irritation	L	L	L	L	L	L
Aquatic Toxicty	L	M	L	L	L	L
Chronic Aquatic Toxicity	L	L	L	*Read across*	dg	L
Persistence	vL	M	*L*	L	L	M
Bioaccumlation	L	L	L	*Read across*	dg	L

Additional alternatives

A few other FCN's have been filed for plasticizers in food contact applications over the past 10 years and are summarized in the table below:

[60] See Malveda, et al. (2018), Footnote 3.

[61] EFSA (European Food Safety Authority) (2006). Opinion of the scientific panel on food additives, flavourings, processing aids and materials in contact with food related to exposure of adults to epoxidised soybean oil used in food contact materials. ESFA Journal 332,1-9.

[62] https://www.cpsc.gov/s3fs-public/ToxicityReviewforEpoxidizedSoybeanOil062019.pdf?LVXyPPxn8xq7shrxW2dBtF_lqU9rGPy_.

Hazard and FCN Summary for Additional Plasticizers

Endpoint	Tri-2-ethylhexyl trimellitate (TOTM)	Castor Oil based	Pentaerythritol tetrapentanoate	Epoxided soya, 2EH esters
CAS No.	3319-31-1	736150-63-3	15834-04-5	68082-34-8
Assessment by:	BASF	BASF	BASF	BASF
FCN/ 21CFR / EFSA*	FCN 1771 (BASF), 50% in vinyl, all food types.	FCN 1126 (Danisco), 50% in vinyl, non-fatty foods, <15% alcohol. EFSA SML = 60 mg/kg (55910)	FCN 1967 (Perstorp), 31% in vinyl, all food types.	FCN 1417 (Galata), 15% in vinyl, aqueous and dry non-fatty foods, <15% alcohol.
Data source	REACH dossier, SDS, other			
Cancer	dg	dg	dg	dg
Mutagenicity	*Low*	Negative	Negative	*L*
Reproductive	Moderate, OECD 421	Low, OECD 416	dg	*Read across*
Developmental	Low, OECD 414	Low, OECD 414	*Read across*	dg
Endocrine Activity	dg	dg	dg	dg
Acute Toxicity	Low	Low	*Read across*	*Read across*
Systemic Toxicity	Low	OECD 408	*Read across*	*Read across*
Neurotoxicity	*Low*	*Low*	dg	dg
Skin Sensitization	Low	Non-sensitizing	*QSAR, Read across*	*Read across*
Respiratory Sensitization	*Low*	*Low*	dg	dg
Skin Irritation	Low	Not irritating	*QSAR, Read across*	*Read across*
Eye Irritation	Low	Not irritating	dg	*Read across*
Aquatic Toxicty	Low	Low	*Read across*	Low
Chronic Aquatic Toxicity	Low	Low	dg	dg
Persistence	Moderate	Readily biodegradable	Readily biodegradable	Readily biodegradable
Bioaccumlation	Moderate	Moderate	*Read across*	*Low, QSAR*

To our knowledge and based on the Carlos, et al. results, these four have limited use in food contact applications, particularly for food packaging. Some also have limited toxicological data; however, FDA data requirements depend on the expected migration into food, and monomeric plasticizers show negligible migration in aqueous and low alcohol foods (i.e., minimal data are required for these uses).

The TCO Certified ASL includes tri-2-ethylhexyl trimellitate (TOTM) based on a Benchmark 2 score by one profiler. We do not have access to the full assessment; however, this appears to be a reasonable conclusion. In addition, TOTM was negative in the rat fetal testosterone screen by EPA (Furr et al., 2014), which suggest the absence of anti-androgenic effects seen with some ortho-phthalates.[63] TOTM also was recently reviewed by CPSC.[64]

The castor oil-based plasticizer (COMGHA) has been reviewed by EFSA and CPSC.[65] There do not appear to be any publicly available assessments for the two other plasticizers, but information is available in the respective REACH dossiers.[66] The pentaerythritol tetrapentanoate recently was added to the ChemFORWARD portfolio based mostly on analog data.

[63] Furr, J. R.; Lambright, C. S.; Wilson, V. S.; Foster, P. M.; Gray, Jr., L. E. "A Short-Term In Vivo Screen Using Fetal Testosterone Product, a Key Event in the Phthalate Adverse Outcome Pathway, to Predict Disruption of Sexual Differentiation," *Toxicol. Sci.*, **2014**, 140, 403-424.

[64] https://www.cpsc.gov/s3fs-public/Toxicity%20Review%20of%20TOTM.pdf?Yjo0hEI05eJsEziyutApCzEobdUITWhX.

[65] https://www.cpsc.gov/s3fs-public/ToxicityReviewforCOMGHA062019.pdf?72HODKVckDhmujTYsOFVPcKfu.vwCMpr.

[66] https://echa.europa.eu/web/guest/information-on-chemicals/registered-substances.

BASF
We create chemistry

7. Human Biomonitoring

Human biomonitoring methods and data are available for four of the non-ortho-phthalate plasticizers discussed in this document, DOTP,[67] DINCH,[68] DEHA,[69] and TOTM.[70] European exposure data are available for all four; U.S. CDC has published U.S. data for DOTP and DINCH. These methods and data are critical for risk assessments and determining general human exposure.

If you have any questions, please contact me at 346-252-4123 or patrick.harmon@basf.com.

Sincerely yours,

J P Harmon

Patrick Harmon, Ph.D.
Industry Manager Industrial Petrochemicals

[67] Lessmann, F; Schuetze, A; Weiss, T.; Langsch, A.; Otter, R.; Bruening, T.; Koch, H.M. Metabolism and Urinary Excretion Kinetics of Di-(2-Ethylhexyl) terephthalate (DEHTP) in Three Male Volunteers After Oral dosage. *Arch. Toxicol.* 2016, 90, 1659 – 1667; and Silva, M.J.; Wong, L-Y; Samandar, E.; Preau, J.L., Jr.; Jia, L.T.; Calafat, A.M. Exposure to Di-2-ethylhexyl Terephthalate in the U.S. General Population from the 2015–2016 National Health and Nutrition Examination Survey. Environ. Int. 2019, 123, 141 – 147.

[68] Schuetze, et al. Additional oxidized and alkyl chain breakdown metabolites of the plasticizer DINCH in urine after oral dosage to human volunteers, *Arch Toxicol,* 2017, 91, 179-188.; and Silva, M. J.; Jia, T.; Samandar, E.; Preau, J. L.; Calafat, A. M. Environmental Exposure to the Plasticizer 1,2-Cyclohexane Dicarboxylic Acid, Diisononyl Ester (DINCH) in US Adults (2000 - 2012), *Environ. Res.*, 2013, 126, 159 - 163. http://dx.doi.org/10.1016/j.envres.2013.05.007.

[69] Nehring, et al. Determination of human urinary metabolites of the plasticizer di(2-ethylhexyl) adipate (DEHA) by online-SPE-HPLC-MS/MS, *J Chromatography B* 2019, 1124, 239-246j.

[70] Hoellerer, et al. Human metabolism and kinetics of tri-(2-ethylhexyl) trimellitate (TEHTM) after oral administration. *Arch Toxicol,* 2018, 92, 2793-2807.

Appendix - Plasticizers Discussed in Comments

Acronym	Names
911P	Linear nonyl, undecyl phthalate
ATBC	Acetyl tributyl citrate
BTHC	Butyryl trihexyl citrate
DEHA	Di-2-ethylhexyl adipate
DIBENZOATES	e.g., dipropylene glycol dibenzoate, diethyleneglycol dibenzoate
DIDP	Diisodecyl phthalate
DINA	Diisononyl adipate
DINCH	Diisononyl cyclohexanedicarboxylate
DINP	Diisononyl phthalate
DOTP or DEHT	Di-2-ethylhexyl terephthalate
DPHP	Dipropylheptyl phthalate
DTDP	Ditridecyl phthalate
DUP	Diundecyl phthalate
ESBO	Epoxidized soy bean oil
TINTM	Triisononyl trimellitate
TOTM	Tri-2-ethylhexyl trimellitate