

September 24th, 2021

EPA Administrator
U.S. Environmental Protection Agency
1201 Constitution Ave NW
Washington, DC 20004
(via <http://www.regulations.gov>)



Dear EPA Administrator,

As per the final rule effective July 29th, 2021 issued under Section 8(d), International Flavors & Fragrances, Inc. (IFF) would like to bring to your attention studies which are known but without possession of copies to assist the EPA in the on-going risk evaluation of 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8- hexamethyl cyclopenta [g]-2-benzopyran (HHCB); Docket No. EPA-HQ-OPPT-2018-0430.

Please see Appendix 1 for the list of studies known to IFF but without possession.

Sincerely,

A handwritten signature in black ink that reads 'Gregory S. Ladics'. The signature is written in a cursive, flowing style.

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Appendix 1: 40 CFR 716.35 (3) Studies which are known but without possession of copies

Avon Products, Inc. 1976d A comparative study of a perfume compound containing 7-acetyl-6-ethyl-1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphthalene (AETT) versus a perfume compound containing 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta (HHCB) in female rats. Unpublished Ref# 13595

Avon Products, Inc. 1976h An evaluation of the ability of various musk chemicals to produce the blue color phenomenon in female rats. Unpublished Ref# 13599

Avon Products, Inc. 1977f Comparative acute toxicity studies in the female rat with five synthetic musk chemicals. Unpublished Ref# 13611

Givaudan 1980r Irritation test with 4-methyl-3-decen-5-ol (Undecavertol B) on the rabbit eye. Unpublished Ref# 49103

Quest International 1977v Determination of the acute oral toxicity of 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-g-2-benzopyran in rats. Unpublished Ref# 46092

Quest International 1978eee Comparison of the acute toxicity of 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-gamma-2-benzopyran; perpetual; and 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane in rats. Unpublished Ref# 49607

Quest International 1980c Phototoxicity tests with 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane (traseolide) and 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-gamma-2-benzopyran (galaxolide) in albino rabbits. Unpublished Ref# 28686

Quest International 1980nnn Guinea pig skin irritation test with 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-g-2-benzopyran. Unpublished Ref# 46093

Quest International 1981gg Guinea pig skin sensitization test with 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-g-2-benzopyran. Unpublished Ref# 46094

Quest International 1986 Phototoxicity study with 5-acetyl-3-isopropyl 1,1,2,6-tetramethylindane (traseolide) and 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-gamma-2-benzopyran (galaxolide) in albino rabbits. Unpublished Ref# 28690

Quest International 1994ccc Assessment of the inherent biodegradability of 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-g-2-benzopyran IPM in the sealed vessel test using acclimatised effluent. Unpublished Ref# 46095

Quest International 1994III The biodegradability of perfume ingredients in the sealed vessel test. Unpublished Ref# 49699



Procter & Gamble Company 2003 Biodegradation of 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-γ-2-benzopyran (Galaxolide (HHCB)) in activated sludge. Unpublished Ref# 54269

PFW Aroma Chemicals B.V. 1996 Biodegradation of polycyclic musks by micro-organisms. Screening of soil samples and investigation of pure cultures. Unpublished Ref# 42919

Api,1999 Research Institute for Fragrance Materials 1999 Evaluation of the oral subchronic toxicity of AHTN and HHCB in the rat. Unpublished report 34482 from Api A.M.; Ford R.A.

Api,1999a Research Institute for Fragrance Materials 1999 Genotoxicity tests with 6-acetyl-1,1,2,4,4,7-hexamethyltetraline and 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-γ-2-benzopyran. Unpublished report 35086 from Api A.M.; San R.H.C.

Api,1999b Research Institute for Fragrance Materials 1999 Evaluation of the oral subchronic toxicity of HHCB (1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-γ-2-benzopyran) in the rat. Unpublished report 35129 from Api A.M.; Ford R.A.

Api,2002 Research Institute for Fragrance Materials 2002 In vitro human skin penetration of the radiolabelled fragrance materials, AHTN and HHCB. Unpublished report 39631 from Api A.M.; Isola D.A.

Api,2013a Research Institute for Fragrance Materials 2013 Disposition and excretion of (14)C-AHTN (7-acetyl-1,1,3,4,4,6-hexamethyl- 1,2,3,4-tetrahydronaphthalene) and (14)C-HHCB (1,3,4,6,7,8-hexahydro- 4,6,6,7,8,8-hexamethyl-cyclopenta- γ-2-benzopyran) after intravenous administration to Sprague-Dawley rats and domestic pigs. Unpublished report 65007 from Api A.M.; Ritacco G.; Sipes I.G.

Blok,1998 Research Institute for Fragrance Materials 1998 Measurement of polycyclic and nitromusks in sludges of sewage treatment plants in The Netherlands. Report to RIFM. Unpublished report 32223 from Blok J.; Balk F.; Sprenger T.

Christian,1997 Research Institute for Fragrance Materials 1997 Oral (gavage) developmental toxicity study of 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethyl cyclopenta-γ-2-benzopyran (HHCB) in rats. Report to RIFM. Unpublished report 31837 from Christian M.S.; Hoberman A.M.; Parker R.M.

Cortes,2003 Research Institute for Fragrance Materials 2003 Indoor air quality evaluation of a plug-in air freshener. Unpublished report 43292 from Cortes D.; Black M.; Halsey J.

Croudace,1997a Research Institute for Fragrance Materials 1997 HHCB: Chronic toxicity to fathead minnow (*Pimephales promelas*) embryos & larvae. Report to RIFM. Unpublished report 30173 from Croudace C.P.; Caunter J.E.; Johnson P.A.

Curry,1995a Research Institute for Fragrance Materials 1995 In vitro mammalian cytogenetic test with 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-γ-2-benzopyran (HHCB). Report to RIFM. Unpublished report 28695 from Curry P.T.; Putman D.L.



DiFrancesco, 2004 Research Institute for Fragrance Materials 2004 Dissipation of fragrance materials in sludge-amended soils. Unpublished report 43828 from DiFrancesco A.M.; Chiu P.C.; Standley L.J.; Allen H.E.; Salvito D.T.

DiFrancesco, 2005 Research Institute for Fragrance Materials 2005 Partition coefficients and volatilization rates of AHTN and HHCB in sludge. Unpublished report 59630 from DiFrancesco A.; Chiu P.; Allen H.

Epstein, 1974 Research Institute for Fragrance Materials 1974 Report on human maximization studies. Report to RIFM. Unpublished report 1801 from Epstein W.L.

Epstein, 1979 Research Institute for Fragrance Materials 1979 Report on human maximization studies. Report to RIFM. Unpublished report 1697 from Epstein W.L.

Federle, 2000 Research Institute for Fragrance Materials 2000 Biotransformation of the polycyclic musk, HHCB, in activated sludge and river water. Unpublished report 36193 from Federle T.W.; Langworthy D.E.; Itrich N.R.; Simonich S.L.

Folk, 1987 Research Institute for Fragrance Materials 1987 Human phototoxicity study of fragrance materials. Report to RIFM. Unpublished report 5744 from Folk C.M.; Dammers K.S.

Forbes, 1978 Research Institute for Fragrance Materials 1978 Phototoxicity and irritation studies of mice and pigs with fragrance materials. Report to RIFM. Unpublished report 2042 from Forbes P.D.; Urbach F.; Davies R.E.

Ford, 1999b Research Institute for Fragrance Materials 1999 Chronic effects of two polycyclic musks on "Pimephales promelas" and "Brachydanio rerio". Unpublished report 38865 from Ford R.A.; Salvito D.T.

Gabriel, 1987a Research Institute for Fragrance Materials 1987 Phototoxicity study in human subjects. Report to RIFM. Unpublished report 5743 from Gabriel K.L.; Mark R.

Gossmann, 1997a Research Institute for Fragrance Materials 1997 Effects of HHCB on reproduction and growth of the earthworm *Eisenia fetida* (Savigny 1826) in artificial soil. Unpublished report 30916 from Gossmann A.; Petto R.

Green, 2001c Research Institute for Fragrance Materials 2001 In-vitro human skin penetration of radiolabelled fragrance material HHCB. Unpublished report 38100 from Green D.M.; Brain S.I.

Gudi, 1997a Research Institute for Fragrance Materials 1997 Micronucleus cytogenetic assay of HHCB in mice. Report to RIFM. Unpublished report 29489 from Gudi R.; Ritter P.

Harbell, 2001 Research Institute for Fragrance Materials 2001 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-g-2-benzopyran: Neutral red uptake phototoxicity assay in Balb/C 3T3 mouse fibroblasts. Report to RIFM. Unpublished report 40274 from Harbell J.W.; Raabe H.A.; Reeves A.; Sizemore A.M.

Harrison, 1986 Research Institute for Fragrance Materials 1986 Phototoxicity testing in human subjects. Unpublished report 5748 from Harrison L.B.; Stolman L.P.



Hawkins,1995d Research Institute for Fragrance Materials 1995 (14)C-HHCB - Studies on the dermal absorption in the rat. Report to RIFM. Unpublished report 27625 from Hawkins D.R.; Kirkpatrick D.; Girkin R.

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Haynes,1984 Research Institute for Fragrance Materials 1984 Primary irritation test in rabbits. Report to RIFM. Unpublished report 1795 from Haynes G.

Haynes,1985 Research Institute for Fragrance Materials 1985 Primary irritation test in rabbits. Report to RIFM. Unpublished report 3099 from Haynes G.

Haynes,1986 Research Institute for Fragrance Materials 1986 Primary irritation test in rabbits. Report to RIFM. Unpublished report 5664 from Haynes G.; Trenchard-Morgan S.

Hopkins,1996a Research Institute for Fragrance Materials 1996 13-Week oral (dietary) toxicity study of HHCB in the rat with a 4 week treatment period. Addendum attached. Report to RIFM. Unpublished report 28070 from Hopkins M.N.; Canning M.; Wright J.A.; Lambert A.H.; Trenchard-Morgan S.

Isola,2003 Research Institute for Fragrance Materials 2003 Exposure characterization from a fragranced plug-in air freshener. Unpublished report 41705 from Isola D.; Smith L.W.; Ansari R.; Black M.S.

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Isola,2004 Research Institute for Fragrance Materials 2004 Exposure characterization from a surrogate fine fragrance. Unpublished report 44448 from Isola D.A.; Rogers R.E.; Myshaniuk A.; Jeng C.-J.; Ansari R.; Smith L.W.

Jones,1996b Research Institute for Fragrance Materials 1996 HHCB: Effects on peri- and post natal development including maternal function in the rat (Gavage administration). Report to RIFM. Unpublished report 28737 from Jones K.; Bottomley A.M.; Gopinath C.

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Kirkpatrick,1997c Research Institute for Fragrance Materials 1997 (14)C-HHCB - Assessment of the fate of a fragrance chemical in the pig after intravenous administration. Report to RIFM. Unpublished report 30511 from Kirkpatrick D.; Elsom L.F.; Girkin R.; Redgrave V.A.

Kirkpatrick,1998 Research Institute for Fragrance Materials 1998 HHCB - Metabolite profiles in rat and pig urine. Report to RIFM. Unpublished report 32550 from Kirkpatrick D.; Girkin R.; Elsom L.F.; Ridgers R.J.

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San,1994c Research Institute for Fragrance Materials 1994 Unscheduled DNA synthesis assay in rat primary hepatocytes with 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-gamma-2-benzopyran (HHCB). Report to RIFM. Unpublished report 28694 from San R.H.C.; Sly J.E.



Schaefer,2005 Research Institute for Fragrance Materials 2005 (14)C-HHCB: Dieaway of a semi-volatile organic compound in river water. Unpublished report 45689 from Wildlife International, Ltd.

Schaefer,2009 Research Institute for Fragrance Materials 2009 (14)C-HHCB: Removal and/or biodegradation of a semi-volatile organic compound in an activated sludge simulation system. Unpublished report 56067 from Schaefer E.C.; Koper C.M.

Schneider,2020 Research Institute for Fragrance Materials 2020 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-γ-2-benzopyran (HHCB): A dietary exposure bioaccumulation test with the bluegill sunfish (*Lepomis macrochirus*). Unpublished report 76882 from Schneider S.Z.; Zhang L.; Martin K.H.; Aufderheide J.A.

Seinen,1997 Research Institute for Fragrance Materials 1997 Estrogenicity of AHTN and HHCB in mice. RIFM report number 31715

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Wolf,1996d Research Institute for Fragrance Materials 1996 HHCB: 21-Day prolonged toxicity study in the bluegill sunfish under flow-through conditions. Report to RIFM. Unpublished report 27682 from Wolf P.U.; Wuthrich V.

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Zhang,2003b Research Institute for Fragrance Materials 2003 Volatilization and partitioning of fragrance materials. Unpublished report 43863 from Zhang S.; Chiu P.C.; Allen H.E.; Salvito D.T.

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Section Sciences et Ingenierie de l'environnement (SIE) 2003 Fate of polycyclic musks during wastewater treatment (II). Unpublished Ref# 49600

The National Institute of Environmental Protection - Baden-Wurttemberg 2003 Schadstoffe in klarschlammgedungenen Ackerboden Baden-Wurttembergs. (Pollutants in klarschlammgedungenen plough land Baden-Wurttembergs). Unpublished Ref# 55551

The Union of German Candle Manufacturers 1997 Investigation of oxidation gases from paraffin aromatic candles in toxicological relevance to classes of damaging materials. Unpublished Ref# 18011