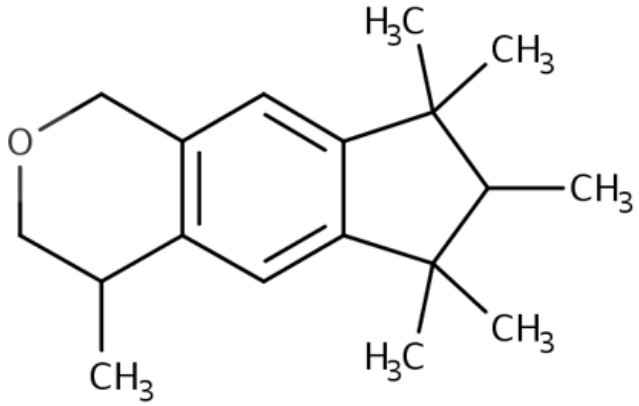
EPA Document# EPA-740-R-20-013
August 2020
Office of Chemical Safety and
Pollution Prevention

United States
Environmental Protection Agency

Final Scope of the Risk Evaluation for 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-Hexamethylcyclopenta[γ]-2-Benzopyran

(HHCB)

CASRN 1222-05-5



August 2020

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ACKNOWLEDGEMENTS

This report was developed by the United States Environmental Protection Agency (U.S. EPA), Office of Chemical Safety and Pollution Prevention (OCSPP), Office of Pollution Prevention and Toxics (OPPT).

Acknowledgements

The OPPT Assessment Team gratefully acknowledges participation or input from Intra-agency reviewers that included multiple offices within EPA, Inter-agency reviewers that included multiple Federal agencies, and assistance from EPA contractors Abt Associates (Contract No. EP-W-16-009), Battelle (Contract No. EP-W-16-017), ERG (Contract No. EP-W-12-006), GDIT (Contract No. HHSN316201200013W), ICF (Contract No. 68HERC19D0003), SRC (Contract No. 68HERH19D0022), and Versar (Contract No. EP-W-17-006). EPA also acknowledges the contributions of technical experts from EPA's Office of Research and Development.

Docket

Supporting information can be found in public docket: EPA-HQ-OPPT-2018-0430.

Disclaimer

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ABBREVIATIONS AND ACRONYMS

ACGIH	American Conference of Governmental Industrial Hygienists
ADAF	Age-dependent adjustment factor
ADME	Absorption, distribution, metabolism and excretion
BP	Boiling point
CAA	Clean Air Act
CASRN	Chemical Abstracts Service registry number
CBI	Confidential business information
CDR	Chemical Data Reporting
CFR	Code of Federal Regulations
COC	Concentration of concern
cP	Centipoise
CPCat	EPA Chemical and Product Categories
DOI	Digital object identifier
EC	Engineering controls
EC_x	Effect concentration (x percent)
ESD	Emission scenario document
EPA	U.S. Environmental Protection Agency
EU	European Union
FR	Federal register
FYI	For your information
HERO	Health and Environmental Research Online
HHCB	1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-Hexamethylcyclopenta[γ]-2-Benzopyran
HHE	Health hazard evaluation
Hr	Hour(s)
Lb	Pound(s)
LC_x	Lethal concentration (x percent)
LOEC	Lowest observed effect concentration
IMIS	Integrated Management Information System
Kg	Kilogram(s)
K_{OC}	Organic carbon-water partition coefficient
K_{OW}	Octanol-water partition coefficient
NIOSH	National Institute for Occupational Safety and Health
NOEC	No observed effect concentration
NWQMC	National Water Quality Monitoring Council
OECD	Organisation for Economic Co-operation and Development
ONU	Occupational non-user
OPPT	Office of Pollution Prevention and Toxics
OSHA	Occupational Safety and Health Administration
PEL	Permissible exposure limit
PECO	Populations, exposures, comparators, and outcomes
PESO	Pathways/processes, exposures, setting/scenario, and outcomes
PESS	Potentially exposed or susceptible subpopulations
PMID	PubMed identifier
POTW	Publicly owned treatment works
PPE	Personal protective equipment
PSD	Particle size distribution
PV	Particle volume

RCRA	Resource Conservation and Recovery Act
RESO	Receptor, exposure, scenario/setting, and outcome
SDS	Safety data sheet
SDWA	Safe Drinking Water Act
SMILES	Simplified Molecular-Input Line-Entry System
$t_{1/2}$	Half-life
TBD	To be determined
TIAB	Title/abstract
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	Time weighted average
USGS	United States Geological Survey
VP	Vapor pressure
WOSid	Web of Science identifier
WWTP	Wastewater treatment plant
Yr	Year

EXECUTIVE SUMMARY

In December 2019, EPA designated 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[γ]-2-benzopyran (HHCB) (CASRN 1222-05-5) as a high-priority substance for risk evaluation following the prioritization process as required by Section 6(b) of the Toxic Substances Control Act (TSCA) and implementing regulations (40 CFR Part 702) (Docket ID: EPA-HQ-OPPT-2019-0131). The first step of the risk evaluation process is the development of the draft scope document. EPA published the *Draft Scope of the Risk Evaluation for 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8- Hexamethylcyclopenta[?]-2-Benzopyran (HHCB) CASRN 1222-05-5* (EPA Document No. EPA-740-D-20-013) (U.S. EPA, 2020b) and provided a 45-day comment period on the draft scope per 40 CFR 702.41(c)(7). EPA has considered comments received during the public comment period (Docket ID: EPA-HQ-OPPT-2018-0430) to inform the development of this final scope document, and public comments received will continue to inform the development of the risk evaluation for HHCB. This document fulfills the TSCA requirement to issue a final scope document per TSCA Section 6(b)(4)(D) and as described in 40 CFR 702.41(c)(8). The scope for HHCB includes the following information: the conditions of use, potentially exposed or susceptible subpopulations (PESS), hazards, and exposures that EPA plans to consider in the risk evaluation, along with a description of the reasonably available information, conceptual model, analysis plan and science approaches, and plan for peer review for this chemical substance.

General Information. HHCB is a synthetic polycyclic musk fragrance with a total annual production volume in the United States between 1 million and < 10 million pounds.

Reasonably Available Information. EPA leveraged the data and information sources already described in the *Proposed Designation of 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-Hexamethylcyclopenta[γ]-2-Benzopyran (HHCB; CASRN 1222-05-5) as a High-Priority Substance for Risk Evaluation* (U.S. EPA, 2019e) to inform the development of this scope document. Furthermore, EPA conducted a comprehensive search to identify and screen multiple evidence streams (*i.e.*, chemistry, fate, release and engineering, exposure, hazard) and the search and screening results are provided in Section 2.1. EPA used the systematic review process described in Appendix A to search for and screen reasonably available information, including information already in EPA's possession, for inclusion in the risk evaluation. This information includes the hazards, exposures, PESS, and conditions of use that may help inform the risk evaluation for HHCB. EPA has focused on the data collection phase (consisting of data search, data screening, and data extraction) during the preparation of the scope document, whereas the data evaluation and integration stages will occur during the development of the risk evaluation and thus are not part of the scoping activities described in this document. EPA plans to consider additional information identified following publication of this scope document, as appropriate, in developing the risk evaluation, including the Chemical Data Reporting (CDR) information that the Agency will receive by the end of November 2020.

Conditions of Use. EPA plans to evaluate manufacturing (including importing), processing, distribution in commerce, commercial and consumer uses, and disposal of HHCB in the risk evaluation. HHCB is manufactured and imported into the United States. HHCB is processed in several ways: incorporated into formulation, mixture, or reaction products; incorporated into articles; repackaged and recycled. HHCB is used as an odor agent in several industrial sectors (*e.g.*, miscellaneous manufacturing; soap, cleaning compound, and toilet preparation manufacturing; plastics material and resin manufacturing; and all other chemical product and preparation manufacturing). HHCB is used in several commercial and consumer products, such as air care products, cleaning and furnishing care products, laundry and dishwashing products, personal care products, plastic and rubber products, and as aroma chemicals. The consumer uses also include uses in paper products. EPA identified these conditions of use from

information reported to EPA though CDR, published literature, public comments, and consultation with stakeholders for both uses currently in production and uses whose production may have ceased. EPA revised the conditions of use in the final scope of the risk evaluation based on additional information collected after publication of the draft scope document for HHCB. EPA did not revise any conditions of use in the final scope document for HHCB based on public comments received on the draft scope. EPA is aware of information reporting use of HHCB in personal care products; however, they are not conditions of use for the chemical substance as defined in TSCA § 3(2) and (4). Section 2.2 provides details regarding the conditions of use within the scope of the risk evaluation.

Conceptual Model. The conceptual models for HHCB are presented in Section 2.6. Conceptual models are graphical depictions of the actual or predicted relationships of conditions of use, exposure pathways (*e.g.*, media), exposure routes (*e.g.*, inhalation, dermal, oral), hazards and receptors throughout the life cycle of the chemical substance. EPA considered reasonably available information as well as public comments received on the draft scope document for HHCB in finalizing the exposure pathways, exposure routes, and hazards EPA plans to evaluate in the risk evaluation. As a result, EPA plans to focus the risk evaluation for HHCB on the following exposures, hazards and receptors:

- *Exposures (Pathways and Routes), Receptors and PESS.* EPA plans to evaluate releases to the environment as well as human and environmental exposures resulting from the conditions of use of HHCB in the risk evaluation. Exposures for HHCB are discussed in Section 2.3. Additional information gathered through systematic review searches will also inform expected exposures.

  EPA's plan for evaluating environmental exposure pathways in the scope of the risk evaluation considers whether other EPA administered statutes and regulatory programs cover HHCB in media pathways falling under the jurisdiction of those authorities. HHCB does not have pathways covered under the jurisdiction of other EPA-administered laws. In Section 2.6.3, EPA presents the conceptual models describing the identified environmental exposures (pathways and routes), receptors and hazards associated with the conditions of use of HHCB within the scope of the risk evaluation.

  EPA considered reasonably available information and comments received on the draft scope for HHCB in determining the human and environmental exposure pathways, routes, receptors and PESS for inclusion in the final scope. EPA plans to evaluate the following human and environmental exposure pathways, routes, receptors and PESS in the risk evaluation:

  - *Occupational exposure:* EPA plans to evaluate exposures to workers and occupational non-users (ONUs) via the inhalation route and exposures to workers via the dermal route associated with the manufacturing, processing, use or disposal of HHCB. EPA plans to analyze dermal exposure for workers and ONUs to mists and dusts that deposit on surfaces.
  - *Consumer and bystander exposure:* EPA plans to evaluate inhalation exposure to HHCB for consumers and bystanders, and dermal exposure to HHCB for consumers during the handling of air care products (*e.g.* aroma chemicals), cleaning and furnishing care products, laundry and dishwashing products, and paper, plastic, and rubber products.
  - *General population exposure:* EPA plans to evaluate general population exposure to HHCB via the oral route from drinking water, surface water, groundwater, fish ingestion, human breast milk and soil, via the inhalation route from ambient air and via dermal route from contact with drinking water, surface water, groundwater and soil.

  - *PESS:* EPA plans to include children, women of reproductive age (*e.g.*, pregnant women), workers, ONUs, consumers, and bystanders as PESS in the risk evaluation.
  - *Environmental exposure:* EPA plans to evaluate exposure to HHCB for aquatic and terrestrial receptors.

- *Hazards.* Hazards for HHCB are discussed in Section 2.4. EPA completed preliminary reviews of information (*e.g.*, federal and international government chemical assessments) to identify potential environmental and human health hazards for HHCB as part of the prioritization (U.S. EPA, 2019e) and scoping process (U.S. EPA, 2020b). EPA also considered reasonably available information collected through systematic review methods as outlined in Appendix A and public comments received on the draft scope for HHCB in determining the broad categories of environmental and human health hazard effects to be evaluated in the risk evaluation. EPA plans to use systematic review methods to evaluate the epidemiological and toxicological literature for HHCB.

  EPA plans to evaluate all potential environmental and human health hazard effects identified for HHCB in Sections 2.4.1 and 2.4.2, respectively. Identified through the data screening phase of systematic review, the potential environmental hazard effects and related information that EPA plans to consider for the risk evaluation include: ADME, cardiovascular, developmental, endocrine, hepatic, mortality, musculoskeletal, neurological, nutritional and metabolic, ocular and sensory, reproductive and skin and connective tissue for HHCB. Similarly, the potential human health hazard effects and related information identified through prioritization and the data screening phase of systematic review for HHCB that EPA plans to consider for the risk evaluation include developmental toxicity, endocrine, mortality, musculoskeletal, reproductive and skin and connective tissue.

Analysis Plan. The analysis plan for HHCB is presented in Section 2.7. The analysis plan outlines the general science approaches that EPA plans to use for the various evidence streams (*i.e.*, chemistry, fate, release and engineering, exposure, hazard) supporting the risk evaluation. The analysis plan is based on EPA's knowledge of HHCB to date, which includes a review of identified information as described in Section 2.1. Should additional data or approaches become reasonably available, EPA may consider them for the risk evaluation.

Peer Review. The draft risk evaluation for HHCB will be peer reviewed. Peer review will be conducted in accordance with relevant and applicable methods for chemical risk evaluations, including using EPA's Peer Review Handbook (U.S. EPA, 2015b) and other methods consistent with Section 26 of TSCA (see 40 CFR 702.45).

1 INTRODUCTION

This document presents the scope of the risk evaluation to be conducted for HHCB under the Frank R. Lautenberg Chemical Safety for the 21st Century Act. The Frank R. Lautenberg Chemical Safety for the 21st Century Act amended TSCA on June 22, 2016. The new law includes statutory requirements and deadlines for actions related to conducting risk evaluations of existing chemicals.

Under TSCA § 6(b), the Environmental Protection Agency (EPA) must designate chemical substances as high-priority substances for risk evaluation or low-priority substances for which risk evaluations are not warranted at the time, and upon designating a chemical substance as a high-priority substance, initiate a risk evaluation on the substance. TSCA § 6(b)(4) directs EPA to conduct risk evaluations for existing chemicals, to "*determine whether a chemical substance presents an unreasonable risk of injury to health or the environment, without consideration of costs or other nonrisk factors, including an unreasonable risk to a potentially exposed or susceptible subpopulation identified as relevant to the risk evaluation by the Administrator under the conditions of use*."

TSCA § 6(b)(4)(D) and implementing regulations require that EPA publish the scope of the risk evaluation to be conducted, including the hazards, exposures, conditions of use and PESS that the Administrator expects to consider, within 6 months after the initiation of a risk evaluation. In addition, a draft scope is to be published pursuant to 40 CFR 702.41. In December 2019, EPA published a list of 20 chemical substances that have been designated high priority substances for risk evaluations (Docket ID: EPA-HQ-OPPT-2019-0131) (84 FR 71924, December 30, 2019), as required by TSCA § 6(b)(2)(B), which initiated the risk evaluation process for those chemical substances. HHCB is one of the chemicals designated as a high priority substance for risk evaluation. On April 9, 2020, EPA published the *Draft Scope of the Risk Evaluation for 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8- Hexamethylcyclopenta[?]-2-Benzopyran (HHCB) CASRN 1222-05-5* (EPA Document No. EPA-740-D-20-013) (U.S. EPA, 2020b) for a 45-day public comment period. After reviewing and considering the public comments received on the draft scope document (Docket ID: EPA-HQ-OPPT-2018-0430), EPA is now publishing this final scope document pursuant to 40 CFR 702.41(c)(8).

2 SCOPE OF THE EVALUATION

2.1 Reasonably Available Information

EPA conducted a comprehensive search for reasonably available information[1] to support the development of this scope document for HHCB. EPA leveraged the data and information sources already collected in the documents supporting the chemical substance's high-priority substance designation. In addition, EPA searched for additional data and information on physical and chemical properties, environmental fate, engineering, exposure, environmental and human health hazards that could be obtained from the following general categories of sources:

1. Databases containing publicly available, peer-reviewed literature;
2. Gray literature, which is defined as the broad category of data/information sources not found in standard, peer-reviewed literature databases;

[1] *Reasonably available information* means information that EPA possesses or can reasonably generate, obtain, and synthesize for use in risk evaluations, considering the deadlines specified in TSCA Section 6(b)(4)(G) for completing such evaluation. Information that meets the terms of the preceding sentence is reasonably available information whether or not the information is confidential business information, that is protected from public disclosure under TSCA Section 14 (40 CFR 702.33).

3. Data and information submitted under TSCA Sections 4, 5, 8(e), and 8(d), as well as "for your information" (FYI) submissions.

Following the comprehensive search, EPA performed a title and abstract screening to identify information potentially relevant for the risk evaluation process. This step also classified the references into useful categories or tags to facilitate the sorting of information through the systematic review process.

Search terms were used to search each of the literature streams and gather HHCB studies. These terms and the methods used to develop them are listed in Appendix A. The studies resulting from the search process were loaded into the EPA Health and Environmental Research Online (HERO) database and then prioritized to screen first the literature likely relevant for each of the disciplines: physical and chemical properties, environmental fate, engineering, exposure and hazard. The tools and methods used to manage the screening process are also outlined in Appendix A. The studies resulting from the search underwent a title/abstract screening process, which tagged them by topic or category. Following this, a determination was made to move studies forward into full-text screening. The criteria used in the screening process for each discipline are found in the population, exposure, comparator, outcome (PECO) statements listed in Appendix A. The screening process results are presented in the form of literature inventory trees and heat maps in Section 2.1.2. The screening process was conducted based on EPA's planning, execution and assessment activities outlined in Appendix A.

EPA has focused on the data collection phase (consisting of data search, data screening, and data extraction) during the preparation of the scope document, whereas the data evaluation and integration stages will occur during the development of the risk evaluation and thus are not part of the scoping activities described in this document.

The subsequent sections summarize the data collection activities completed to date for the general categories of sources and topic areas (or disciplines) using systematic review methods.

2.1.1 Search of Gray Literature

EPA surveyed the gray literature[2] and identified 29 search results relevant to EPA's risk evaluation needs for HHCB. Appendix A.3.4 lists the gray literature sources that yielded 29 discrete data or information sources relevant to HHCB. EPA further categorized the data and information into the various topic areas (or disciplines) supporting the risk evaluation (*e.g.*, physical and chemical properties, environmental fate, ecological hazard, human health hazard, exposure, engineering), and the breakdown is shown in Figure 2-1. EPA plans to consider additional reasonably available information from gray literature if it becomes available during the risk evaluation phase.

[2] Gray literature is defined as the broad category of data/information sources not found in standard, peer-reviewed literature databases (*e.g.*, PubMed and Web of Science). Gray literature includes data/information sources such as white papers, conference proceedings, technical reports, reference books, dissertations, information on various stakeholder websites, and other databases.

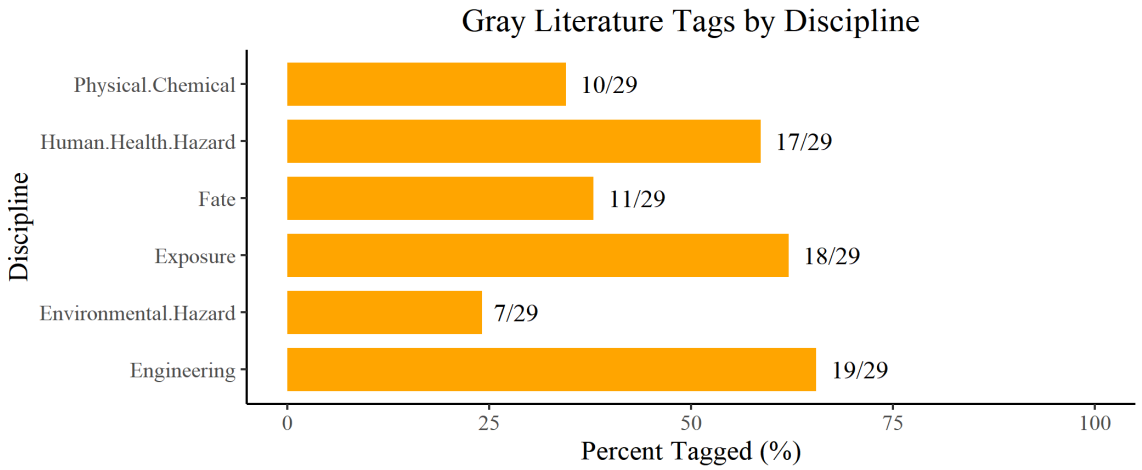


Figure 2-1. Gray Literature Tags by Discipline for HHCB
The percentages across disciplines do not add up to 100%, as each source may provide data or information for multiple disciplines.

2.1.2 Search of Literature from Publicly Available Databases (Peer-Reviewed Literature)

EPA has begun the systematic review process and has conducted searching and screening of the reasonably available literature using the process outlined in Appendix A. This includes performing a comprehensive search of the reasonably available peer review literature on physical and chemical properties, environmental fate and transport, engineering (environmental release and occupational exposure), exposure (environmental, general population and consumer) and environmental and human health hazards of HHCB. Eligibility criteria were applied in the form of PECO statements (see Appendix A.2.1). Included references met the PECO criteria, whereas excluded references did not meet the criteria (*i.e.*, not relevant), and supplemental material was considered as potentially relevant (see Appendix A.2). EPA plans to analyze the reasonably available information identified for each discipline during the development of the risk evaluation.

EPA created literature inventory trees to graphically illustrate the flow of data and information sources following full-text screening (see Figure 2-2; Figure 2-3; Figure 2-5; Figure 2-7; and Figure 2-9). EPA used the Health Assessment Workplace Collaborative (HAWC) tool to develop web-based literature inventory trees illustrating, through interactive links, studies that were included or excluded. These literature inventory trees enhance the transparency of the decisions resulting from the screening process described in Appendix A. For each of the corresponding disciplines, the literature was tagged to be included for evaluation during the risk evaluation. The literature inventory tree for physical and chemical properties is provided as a static diagram (Figure 2-2). For all other disciplines, static screen captures are provided in addition to links within each figure's caption to the interactive trees. The links show individual studies that were tagged as included, excluded, or supplemental. Supplemental studies did not meet all inclusion criteria, but may be considered during the risk evaluation as supporting information (see Appendix A). These studies can be accessed through the hyperlink provided in the associated caption below each figure. In some figures, the sum of the numbers for the various sub-categories may be larger than the broader category because some studies may be included under multiple sub-categories. In other cases, the sum of the various sub-categories may be smaller than the main category because some studies may not be depicted in the sub-categories if their relevance to the risk evaluation was unclear.

In addition, EPA tabulated the number and characteristics of the data and information sources included in the full-text screening process in the form of literature inventory heat maps for the fate, engineering, exposure and hazard disciplines (see Figure 2-4; Figure 2-6; Figure 2-8; and Figure 2-10) For each of these four disciplines, a static image of the literature inventory heat map is provided, and a link to the interactive version presented in HAWC is included in the caption below each diagram.

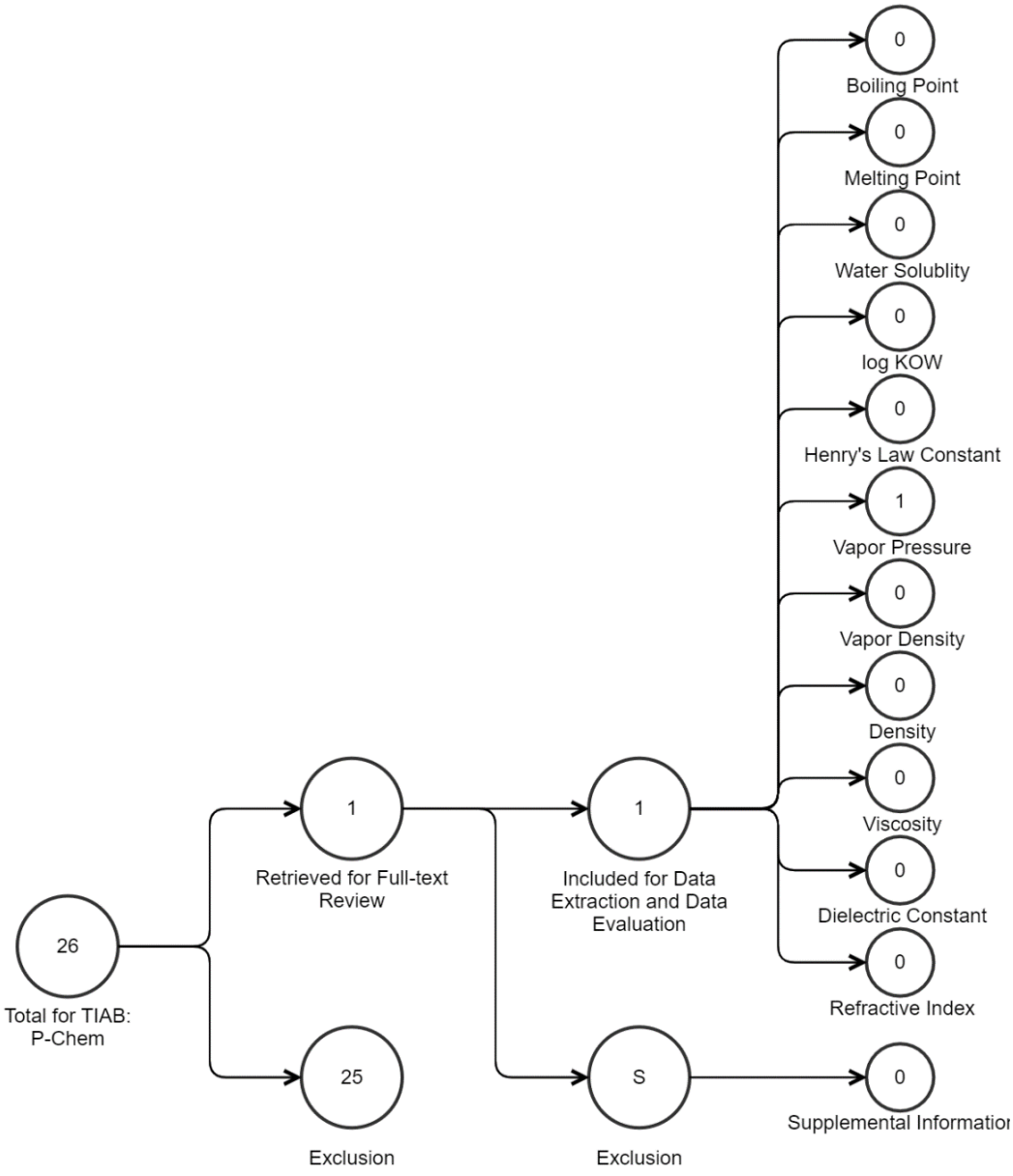


Figure 2-2. Peer-Reviewed Literature Inventory Tree – Physical and Chemical Properties Search Results for HHCB

Data in this static figure represents references obtained from the publicly available databases search (see Appendix A.1.2) that were included during full-text screening as of June 2, 2020. TIAB refers to "title and abstract" screening.

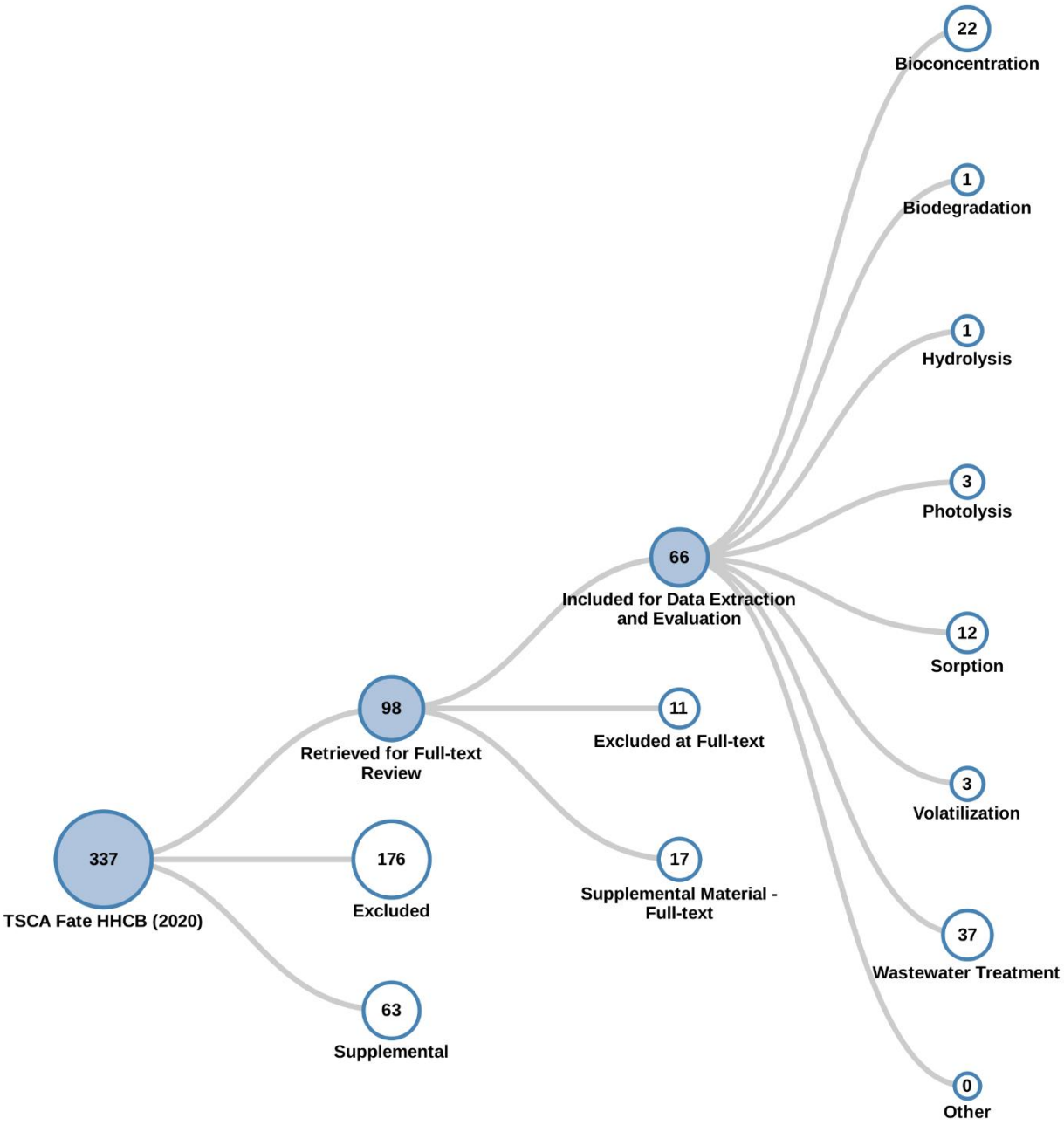


Figure 2-3. Peer-Reviewed Literature Inventory Tree – Fate and Transport Search Results for HHCB

Click here to view the interactive literature inventory tree. Data in this figure represent references obtained from the publicly available databases search (see Appendix A.1.2) that were included during full-text screening as of June 2, 2020. Additional data may be added to the interactive version of this diagram as they become available.

	Media					
Endpoint	Air	Soil, Sediment	Wastewater, Biosolids	Water	Other	Grand Total
Bioconcentration	1	13	7	17		22
Biodegradation			1			1
Hydrolysis	1					1
Photolysis	2		1	2		3
Sorption	1	7	7	8		12
Volatilization	1	1	1	3		3
Wastewater Treatment	2	10	37	33		37
Grand Total	6	26	44	54		66

Figure 2-4. Peer-reviewed Literature Inventory Heat Map – Fate and Transport Search Results for HHCB

Click here to view the interactive version for additional study details. The column totals, row totals, and grand totals indicate total numbers of unique references, as some references may be included in multiple cells. The various shades of color visually represent the number of relevant references identified by media or endpoint. The darker the color, the more references are available for a given media or endpoint. Data in this figure represents references obtained from the publicly available databases search (see Appendix A.1.2) that were included during full-text screening as of June 2, 2020. Additional data may be added to the interactive version of this heat map as they become available.

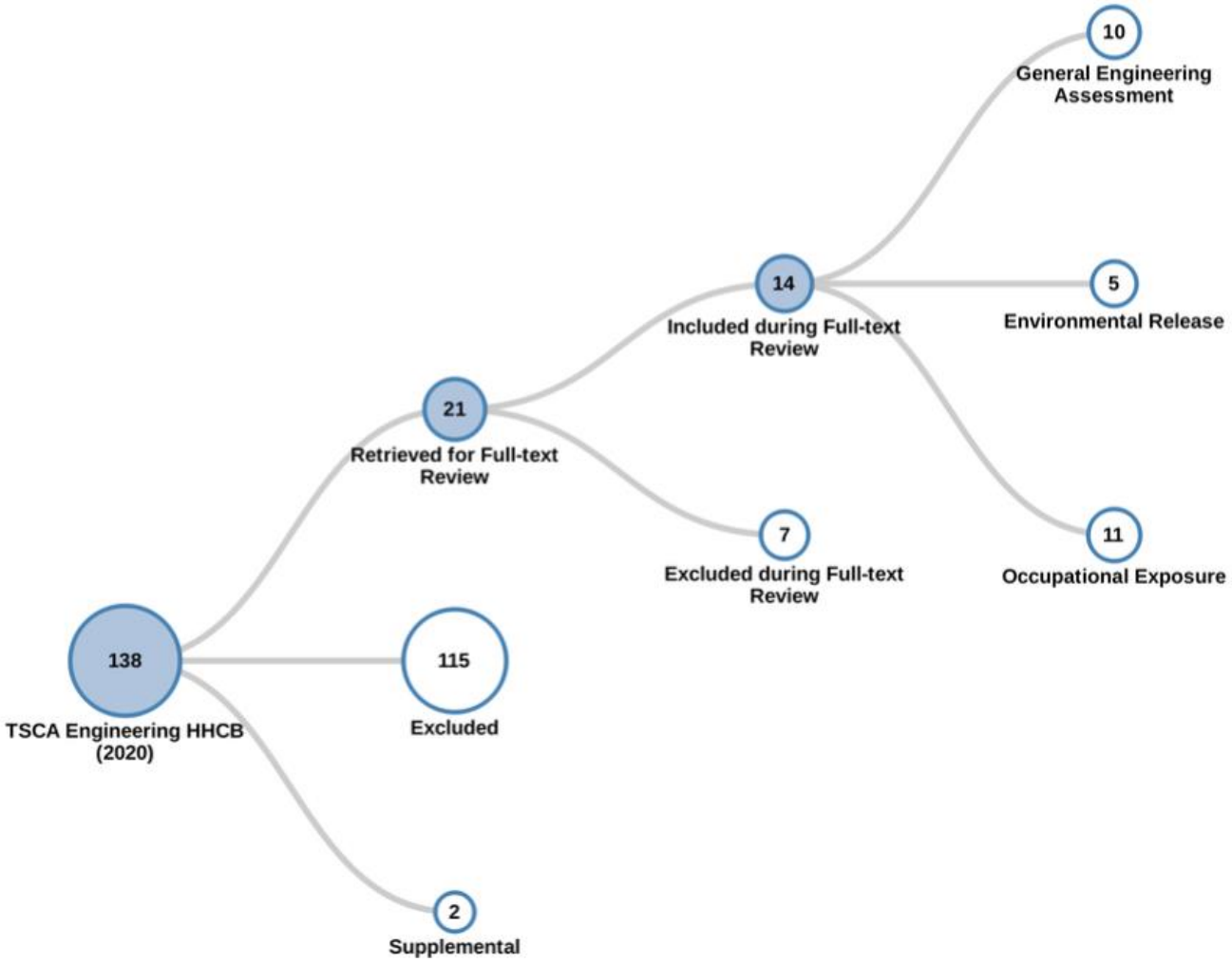


Figure 2-5. Peer-reviewed Literature Inventory Tree – Engineering Search Results for HHCB
Click here to view the interactive literature inventory tree. Data in this figure represent references obtained from the publicly available databases search (see Appendix A.1.2) that were included during full-text screening as of August 5, 2020. Additional data may be added to the interactive version of this figure as they become available.

Data Type	Evidence Tags	
Environmental Releases	Description of release source	5
	Release frequency	1
	Release or emission factors	3
	Release quantity	2
	Waste treatment methods and pollution control	2
	Total	5
General Engineering Assessment	Chemical concentration	5
	Life cycle description	1
	Number of sites	2
	Process description	4
	Production, import, or use volume	5
	Throughput	2
	Total	10
Occupational Exposures	Area sampling data	6
	Dermal exposure data	4
	Engineering control	1
	Exposure duration	3
	Exposure frequency	2
	Exposure route	6
	Number of workers	3
	Particle size characterization	
	Personal protective equipment	3
	Personal sampling data	1
	Physical form	4
	Worker activity description	2
	Total	11
Grand Total		14

Figure 2-6. Peer-reviewed Literature Inventory Heat Map – Engineering Search Results for HHCB

Click here to view the interactive version for additional study details. Data in this figure represent references obtained from the publicly available databases search (see Appendix A.1.2) that were included during full-text screening as of August 5, 2020. Additional data may be added to the interactive version as they become available.

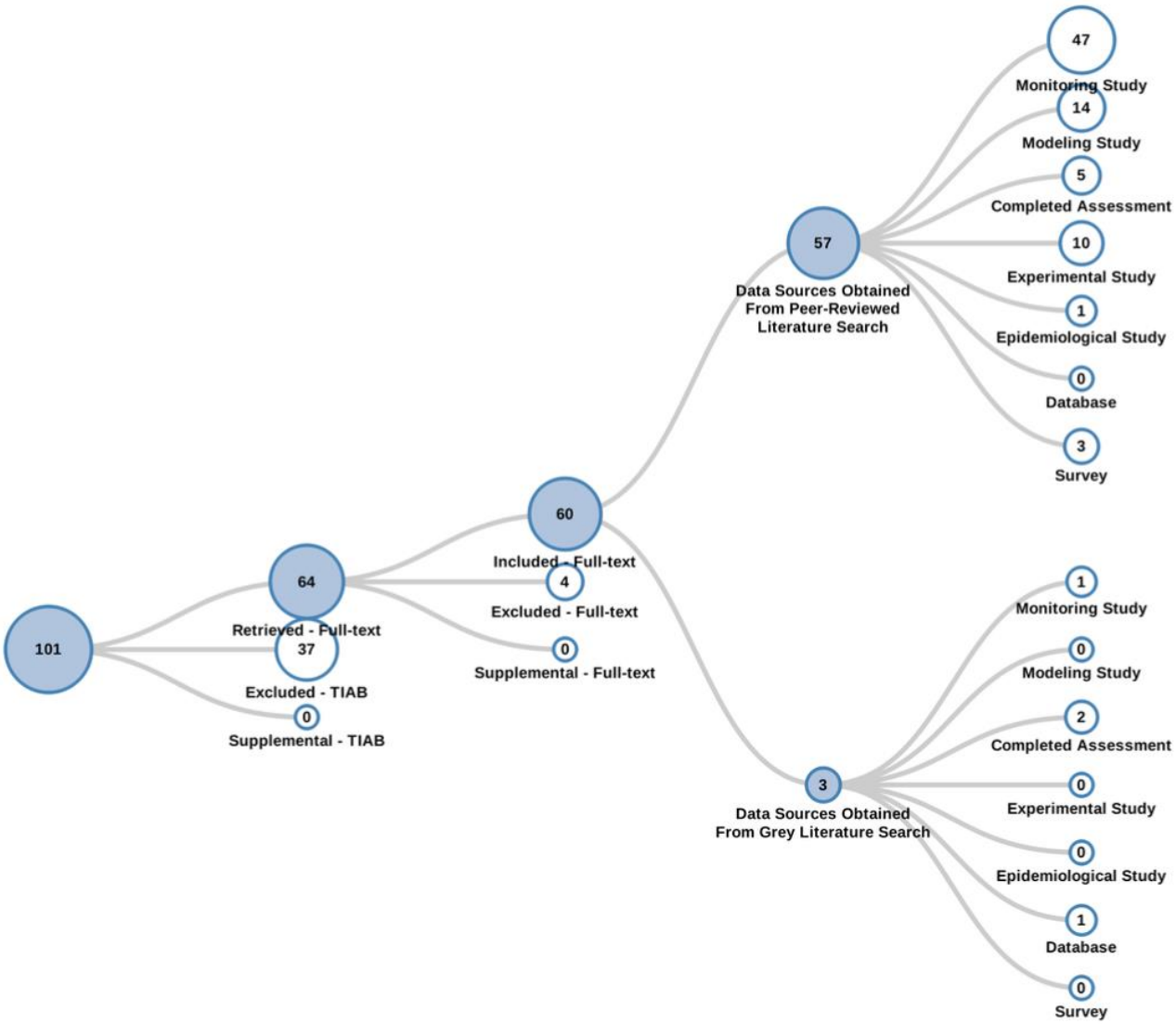


Figure 2-7. Peer-Reviewed and Gray Literature Inventory Tree – Exposure Search Results for HHCB

Click here to view the interactive literature inventory tree. Data in this figure represent all references obtained from the publicly available databases search (see Appendix A.1.2), and gray literature references search (see Appendix A.3) that were included during full-text screening as of July 31, 2020. Additional data may be added to the interactive version as they become available.

Media (group)	Data Type: Monitoring Study	Modeling Study	Completed Assessment	Experimental Study	Epidemiological Study	Database	Survey	Grand Total
Ambient Air	1		2					3
Biosolids/Sludge	2	1	1	1				3
Drinking Water			1					1
Groundwater			1					1
Land Disposal/ Landfill			1					1
Sediment	2	1	1	1				3
Soil	1	1	2					3
Surface Water	6	2	1	2		1		7
Wastewater	3		1	1				4
Aquatic Species	5		2					6
Terrestrial Species			1					1
Consumer	7	4	3	8				14
Dietary	6	2	2	1				8
Dust	9	7	1				1	12
Exposure Factors	1	2	1					2
Exposure Pathway			1				1	2
Human Biomonitoring	13	1	2		1		1	14
Indoor Air	14	6	3	1			1	19
Isomers								
Use Information			1				1	2
No Evidence Type								
Grand Total	48	14	7	10	1	1	3	60

Figure 2-8. Peer-reviewed and Gray Literature Inventory Heat Map – Exposure Search Results for HHCB

Click here to view the interactive version for additional study details. The column totals, row totals, and grand totals indicate total numbers of unique references, as some references may be included in multiple cells. The various shades of color visually represent the number of relevant references identified by exposure media or data type. The darker the color, the more references are available for a given exposure media or data type. Data in this figure represent all references obtained from the publicly available databases search (see Appendix A.1.2), and gray literature references search (see Appendix A.3) that were included during full-text screening as of July 31, 2020. Additional data may be added to the interactive version of this figure as they become available.

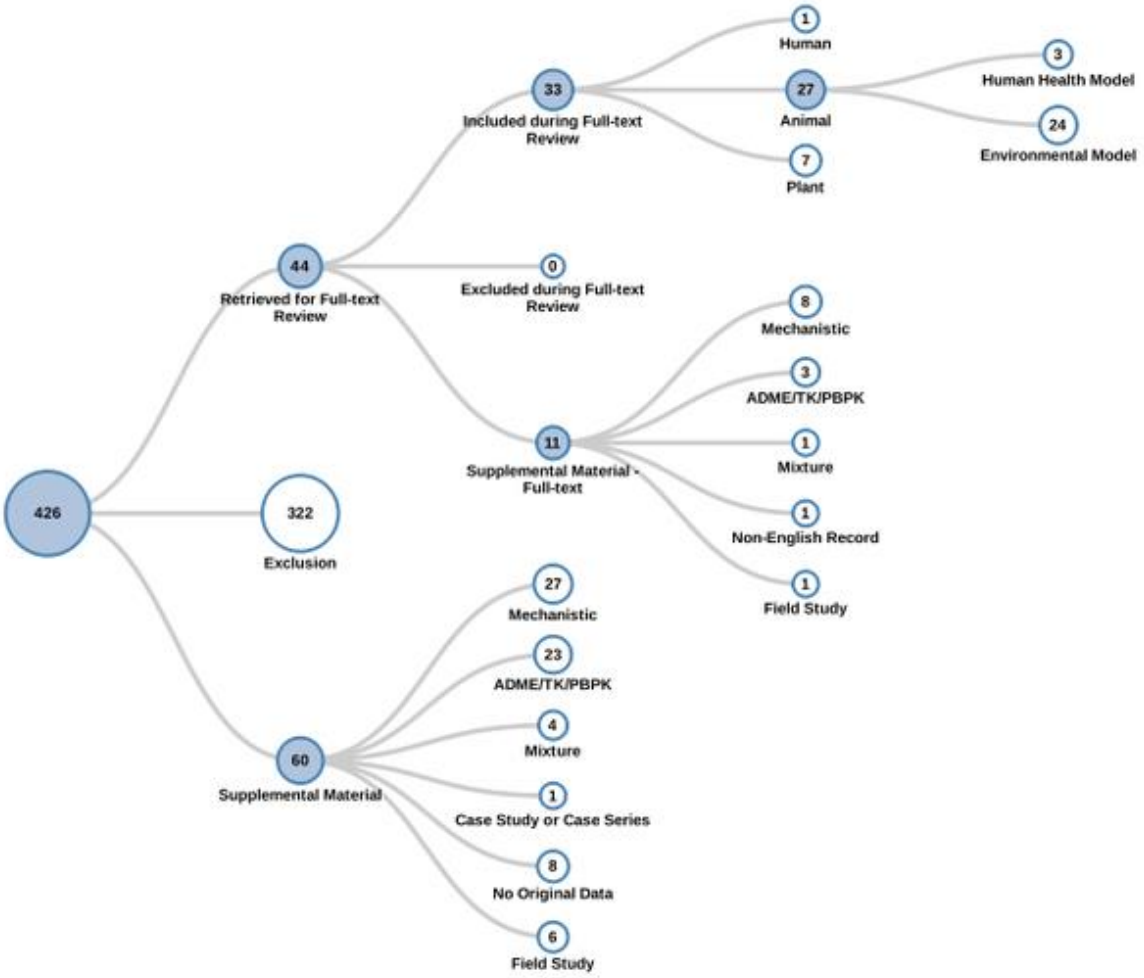


Figure 2-9. Peer-reviewed Literature Inventory Tree – Human Health and Environmental Hazards Search Results for HHCB

Click here to view the interactive literature inventory tree. Data in this figure represent references obtained from the publicly available databases search (see Appendix A.1.2) that were included during full-text screening as of June 10, 2020. Additional data may be added to the interactive version of this figure as they become available.

	Evidence Type				
Health Outcomes	Human	Animal - Human Health Model	Animal - Environmental Model	Plant	Grand Total
ADME			3	2	4
Cancer					
Cardiovascular			1		1
Developmental		1	8	3	11
Endocrine		1	4	1	6
Gastrointestinal					
Hematological and Immune					
Hepatic			2		2
Mortality		1	8		9
Musculoskeletal		1	1		2
Neurological			2		2
Nutritional and Metabolic			4	2	6
Ocular and Sensory			1		1
PBPK					
Renal					
Reproductive		2	4		6
Respiratory					
Skin and Connective Tissue	1		2		3
No Tag		1	4	2	6
Grand Total	1	3	24	7	33

Figure 2-10. Peer-reviewed Literature Inventory Heat Map – Human Health and Environmental Hazards Search Results for HHCB

Click here to view the interactive version for additional study details. The numbers indicate the number of studies with TIAB keywords related to a particular health outcome, not the number of studies that observed an association with HHCB. Evidence types were manually extracted, and Health Systems were determined via machine learning. Therefore, the studies examining multiple Health Outcomes and Evidence types, connections between health outcome, and evidence type may not be accurately represented. If a study evaluated multiple health outcomes or included multiple populations or study designs, it is shown here multiple times. Data in this figure represents references obtained from the publicly available databases search (see Appendix A.1.2) that were included during full-text screening as of June 10, 2020. Additional data may be added to the interactive version as they become available.

2.1.3 Search of TSCA Submissions

Table 2-1 presents the results of screening the titles of data sources and reports submitted to EPA under various sections of TSCA. EPA screened a total of one submission using PECO or similar statements that identify inclusion/exclusion criteria specific to individual disciplines (see Table 2-1 for the list of disciplines). The details about the criteria are presented in Appendix A.2.1. EPA identified one submission that met the inclusion criteria in these statements and identified zero submissions with supplemental data. EPA excluded zero submissions.

Table 2-1. Results of Title Screening of Submissions to EPA under Various Sections of TSCA

Discipline	Included	Supplemental[a]
Physical and Chemical Properties	0	0
Environmental Fate and Transport	0	0
Environmental and General Population Exposure	0	0
Occupational Exposure/Release Information	0	0
Environmental Hazard	0	0
Human Health Hazard	1	0

[a] Included submissions may contain supplemental data for other disciplines, which will be identified at full-text review.

2.2 Conditions of Use

As described in the *Proposed Designation of 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-Hexamethylcyclopenta[γ]-2-Benzopyran (HHCB; CASRN 1222-05-5) as a High-Priority Substance for Risk Evaluation* (U.S. EPA, 2019e), EPA assembled information from the Chemical Data Reporting (CDR) program to determine conditions of use[3] or significant changes in conditions of use of the chemical substance. Once the 2020 CDR reporting period ends in November 2020, EPA plans to utilize the most recent CDR information. EPA also consulted a variety of other sources to identify uses of HHCB, including published literature, company websites, and government and commercial trade databases and publications. To identify formulated products containing HHCB, EPA searched for safety data sheets (SDS) using internet searches, EPA Chemical and Product Categories (CPCat) data (U.S. EPA, 2019d), and other resources in which SDSs could be found. SDSs were cross-checked with company websites to make sure that each product SDS was current. In addition, EPA incorporated communications with companies, industry groups, and public comments to supplement the condition of use information.

EPA identified and described the categories and subcategories of conditions of use that EPA plans to consider in the risk evaluation (Section 2.2.1; Table 2-2). The conditions of use included in the scope of the risk evaluation are those reflected in the life cycle diagrams and conceptual models.

After gathering reasonably available information related to the manufacture, processing, distribution in commerce, use, and disposal of HHCB, EPA identified those activities for HHCB the Agency determined not to be conditions of use or will otherwise be excluded during scoping. These activities are described in Section 2.2.2.

2.2.1 Categories and Subcategories of Conditions of Use Included in the Scope of the Risk Evaluation

Table 2-2 lists the conditions of use that are included in the scope of the risk evaluation.

[3] *Conditions of use* means the circumstances, as determined by the Administrator, under which a chemical substance is intended, known, or reasonably foreseen to be manufactured, processed, distributed in commerce, used, or disposed of (TSCA § 3(4)).

Table 2-2. Categories and Subcategories of Conditions of Use Included in the Scope of the Risk Evaluation

Life Cycle Stage [a]	Category [b]	Subcategory [c]	Reference
Manufacturing	Domestic manufacturing	Domestic manufacturing	U.S. EPA (2019b)
	Importing	Importing	U.S. EPA (2019b)
Processing	Processing – incorporation into formulation, mixture or reaction product	Odor agent (in all other chemical product and preparation manufacturing; miscellaneous manufacturing; soap, cleaning compound, and toilet preparation manufacturing; other: fragrance mixtures and fragrance raw material)	U.S. EPA (2019b)
	Processing – incorporation into articles	Odor agent (in plastics material and resin manufacturing)	U.S. EPA (2019b)
	Repackaging	Odor agent (in all other chemical product and preparation manufacturing)	U.S. EPA (2019b)
	Recycling	Recycling	U.S. EPA (2019b)
Distribution in commerce	Distribution in commerce	Distribution in commerce	
Commercial Use	Air care products (*e.g.*, aroma chemicals)	Air fresheners for motor vehicles	U.S. EPA (2019b)
		Continuous action air fresheners (*e.g.*, scented candles and solid/gel air fresheners)	U.S. EPA (2019b);EPA-HQ-OPPT-2018-0430-0012
		Instant action air fresheners (aerosol and sprays)	U.S. EPA (2019b); EPA-HQ-OPPT-2018-0430-0012
	Cleaning and furnishing care products	Cleaning products, including all-purpose liquid cleaner and bathroom cleaners (including liquid, foam, and spray cleaners)	U.S. EPA (2019b)
	Laundry and dishwashing products	Laundry products, including liquid laundry detergent and fabric softener	U.S. EPA (2019b);EPA-HQ-OPPT-2018-0430-0013
	Plastic and rubber products not covered elsewhere	Plastic and rubber products	U.S. EPA (2019b)

Life Cycle Stage [a]	Category [b]	Subcategory [c]	Reference
	Other use	Laboratory chemicals	Sigma-Aldrich (2019)
Consumer use	Air care products (*e.g.*, aroma chemicals)	Air fresheners for motor vehicles	U.S. EPA (2019b)
		Continuous action air fresheners (*e.g.*, scented candles)	U.S. EPA (2019b);EPA-HQ-OPPT-2018-0430-0012
		Instant action air fresheners (aerosol and sprays)	U.S. EPA (2019b);EPA-HQ-OPPT-2018-0430-0012
	Cleaning and furnishing care products	Cleaning products, including all-purpose liquid cleaner and bathroom cleaners (including liquid, foam, and spray cleaners)	U.S. EPA (2019b)
	Laundry and dishwashing products	Laundry products, including liquid laundry detergent and fabric softener	U.S. EPA (2019b);EPA-HQ-OPPT-2018-0430-0013
	Paper products	Paper products	U.S. EPA (2019b)
	Plastic and rubber products not covered elsewhere	Plastic and rubber products	U.S. EPA (2019b)
Disposal	Disposal	Disposal	

a. Life Cycle Stage Use Definitions (40 CFR § 711.3)
- "Industrial use" means use at a site at which one or more chemicals or mixtures are manufactured (including imported) or processed. In the *Proposed Designation of 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-Hexamethylcyclopenta[γ]-2-Benzopyran (HHCB; CASRN 1222-05-5) as a High-Priority Substance for Risk Evaluation* (U.S. EPA, 2019e), there is an industrial use reported for HHCB as surface active agent. After further communication with the industry reporting the use, EPA has concluded that the correct classification of the use of HHCB is "commercial use" and "consumer use" in cleaning and furnishing care products and in laundry and dishwashing products (EPA-HQ-OPPT-2018-0430-0018).
- "Commercial use" means the use of a chemical or a mixture containing a chemical (including as part of an article) in a commercial enterprise providing saleable goods or services.
- "Consumer use" means the use of a chemical or a mixture containing a chemical (including as part of an article, such as furniture or clothing) when sold to or made available to consumers for their use.
- Although EPA has identified both industrial and commercial uses here for purposes of distinguishing scenarios in this document, the Agency interprets the authority over "any manner or method of commercial use" under TSCA Section 6(a)(5) to reach both.

b. These categories of conditions of use appear in the Life Cycle Diagram, reflect CDR codes, and broadly represent conditions of use of HHCB in industrial and/or commercial settings.

c. These subcategories reflect more specific conditions of use of HHCB.

In the final scope, EPA made the following change to the conditions of use:
- Aerosol products were removed as examples for the cleaning and furnishing care products since after further research regarding cleaning and furnishing care products, aerosol products were not identified.

2.2.2 Activities Excluded from the Scope of the Risk Evaluation

As explained in the final rule for *Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act* (82 FR 33726, July 20, 2017), TSCA Section 6(b)(4)(D) requires EPA to identify the hazards, exposures, conditions of use, and the PESS the Administrator expects to consider in a risk evaluation, suggesting that EPA may exclude certain activities that it determines to be conditions of use on a case-by-case basis (82 FR 33736, 33729; July 20, 2017). TSCA Section 3(4) also grants EPA discretion to determine the circumstances that are appropriately considered to be conditions of use for a particular chemical substance[4]. As a result, EPA does not plan to include in this scope or in the risk evaluation activities described below that the Agency does not consider to be conditions of use or for which EPA is exercising discretionary authority provided by TSCA Section 6(b)(4)(D).

TSCA Section 3(2) also excludes from the definition of "chemical substance" "any food, food additive, drug, cosmetic, or device (as such terms are defined in Section 201 of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 321]) when manufactured, processed, or distributed in commerce for use as a food, food additive, drug, cosmetic, or device" as well as "any pesticide (as defined in the Federal Insecticide, Fungicide, and Rodenticide Act [7 U.S.C. 136 et seq.]) when manufactured, processed, or distributed in commerce for use as a pesticide." EPA has determined that the following uses of HHCB are non-TSCA uses:

HHCB is used in personal care products intended for use as cosmetics. After reviewing the public comments received (EPA-HQ-OPPT-2018-0430-0028) on the proposed designation (U.S. EPA, 2019e) and additional outreach to the commenters and comments from the U.S. Food and Drug Administration, EPA has determined that HHCB use in personal care products intended for use as cosmetics, including soaps, falls outside TSCA's definition of "chemical substance." Under TSCA § 3(2)(B)(vi), the definition of "chemical substance" does not include any food, food additive, drug, cosmetic, or device (as such terms are defined in Section 201 of the Federal Food, Drug, and Cosmetic Act) when manufactured, processed, or distributed in commerce for use as a food, food additive, drug, cosmetic, or device. Activities and releases associated with such personal care products use are therefore not "conditions of use" (defined as circumstances associated with "a chemical substance," TSCA § 3(4)) and will not be evaluated during risk evaluation.

2.2.3 Production Volume

As reported to EPA during the 2016 CDR reporting period and described here as a range to protect production volumes that were claimed as confidential business information (CBI), total production volume of HHCB in 2015 was between 1 million and less than 10 million pounds (U.S. EPA, 2017). EPA also considered pre-2015 CDR production volume information, as detailed in the *Proposed Designation of 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-Hexamethylcyclopenta[γ]-2-Benzopyran (HHCB; CASRN 1222-05-5) as a High-Priority Substance for Risk Evaluation* (U.S. EPA, 2019e) and will

[4] *Chemical substance* means any organic or inorganic substance of a particular molecular identity, including any combination of such substances occurring in whole or in part as a result of a chemical reaction or occurring in nature, and any element or uncombined radical. Chemical substance does not include (1) any mixture; (2) any pesticide (as defined in the Federal Insecticide, Fungicide, and Rodenticide Act) when manufactured, processed, or distributed in commerce for use as a pesticide; (3) tobacco or any tobacco product; (4) any source material, special nuclear material, or byproduct material (as such terms are defined in the Atomic Energy Act of 1954 and regulations issued under such Act); (5) any article the sale of which is subject to the tax imposed by Section 4181 of the Internal Revenue Code of 1954 (determined without regard to any exemptions from such tax provided by Section 4182 or 4221 or any other provision of such Code), and; (6) any food, food additive, drug, cosmetic, or device (as such terms are defined in Section 201 of the Federal Food, Drug, and Cosmetic Act) when manufactured, processed, or distributed in commerce for use as a food, food additive, drug, cosmetic, or device (TSCA § 3(2)).

include more recent production volume information from the 2020 CDR reporting period in the risk evaluation to support the environmental release and exposure assessment.

2.2.4 Overview of Conditions of Use and Lifecycle Diagram

Figure 2-11 provides the lifecycle diagram for HHCB. The life cycle diagram is a graphical representation of the various life stages of the industrial, commercial and consumer use categories included within the scope of the risk evaluation. The information in the life cycle diagram is grouped according to the CDR processing codes and use categories (including functional use codes for industrial uses and product categories for industrial, commercial and consumer uses). Appendix E contains more detailed descriptions (*e.g.*, process descriptions, worker activities, process flow diagrams) for each manufacturing, processing, distribution in commerce, use and disposal category.

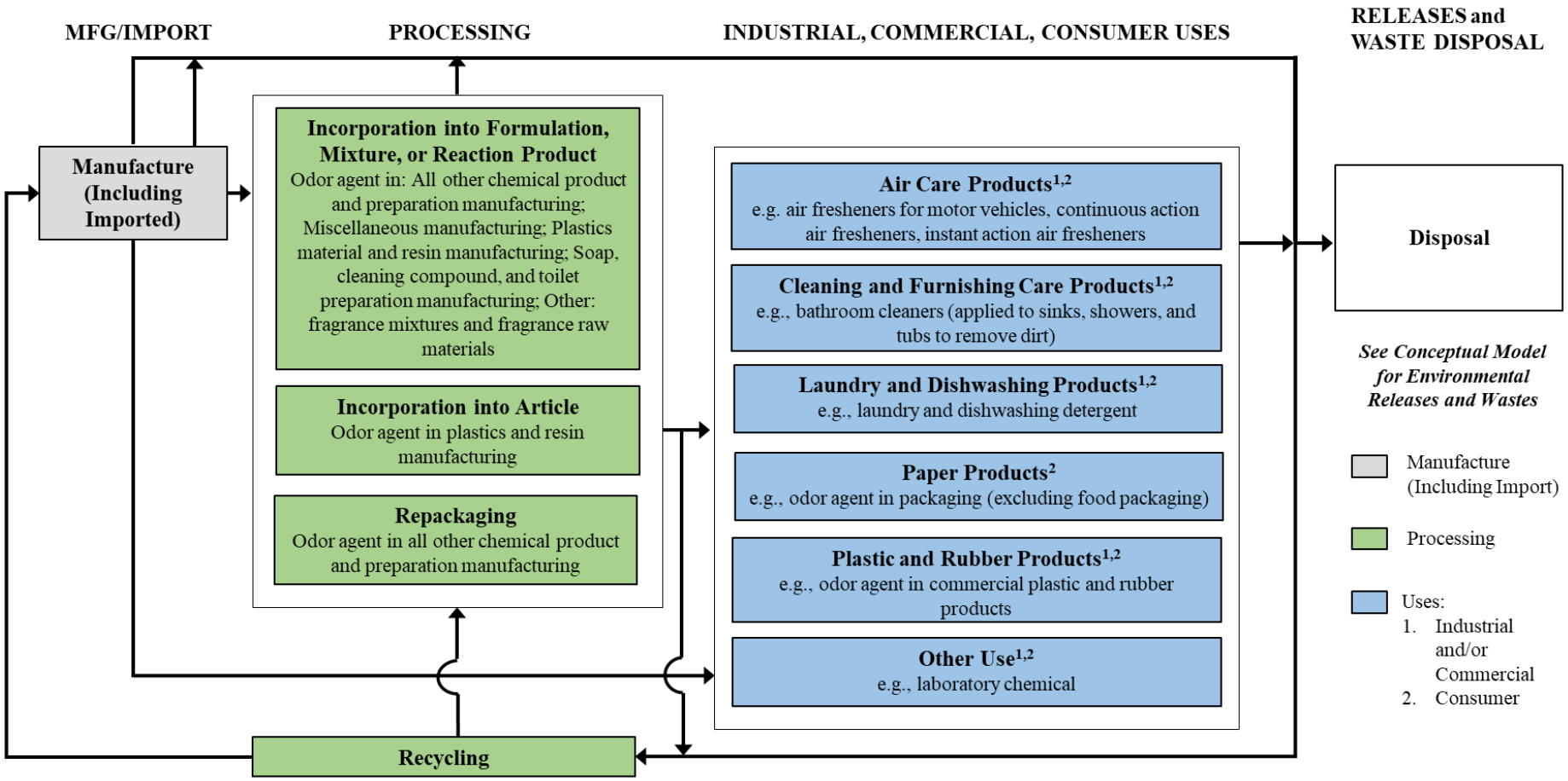


Figure 2-11. HHCB Life Cycle Diagram

2.3 Exposures

For TSCA exposure assessments, EPA plans to analyze human and environmental exposures and releases to the environment resulting from the conditions of use within the scope of the risk evaluation for of HHCB. In this section, the physical and chemical properties, environmental fate and transport properties and releases to the environment are described in addition to potential human and environmental exposures from TSCA conditions of use and from other possible or known sources. Release pathways and routes will be described in Section 2.6 to characterize the relationship or connection between the conditions of use of the chemical and the exposure to human receptors, including PESS, and environmental receptors. EPA plans to consider, where relevant, the duration, intensity (concentration), frequency, and number of exposures in characterizing exposures to HHCB.

2.3.1 Physical and Chemical Properties

Consideration of physical and chemical properties is essential for a thorough understanding or prediction of environmental fate (*i.e.*, transport and transformation) and the eventual environmental concentrations. It can also inform the hazard assessment. Table 2-3 summarizes the physical and chemical property values preliminarily selected for use in the risk evaluation from among the range of reported values collected as of June 2020. This information differs from that presented in the *Proposed Designation of 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-Hexamethylcyclopenta[γ]-2-Benzopyran (HHCB; CASRN 1222-05-5) as a High-Priority Substance for Risk Evaluation* (U.S. EPA, 2019e) and may be updated as EPA continues to evaluate and integrate additional information through systematic review methods. Figure 2-12 summarizes the distribution of reported values for eight physical and chemical properties routinely used in existing chemical risk evaluations. Appendix B presents summary statistics for reported physical and chemical property values. All physical and chemical property values that were extracted and evaluated as of June 2020 are presented in the supplemental file *Data Extraction and Data Evaluation Tables for Physical and Chemical Property Studies* (EPA-HQ-OPPT-2018-0430).

Table 2-3. Physical and Chemical Properties of HHCB

Property or Endpoint	Value[a]	Reference	Data Quality Rating
Molecular formula	$C_{18}H_{26}O$	NA	NA
Molecular weight	258.41 g/mol	NA	NA
Physical state	Viscous liquid	NLM (2018)	High
Physical properties	Colorless, strong musk odor	NLM (2018)	High
Melting point	-5°C	U.S. EPA (2019c)	High
Boiling point	325°C	U.S. EPA (2019c)	High
Density	1.0054 g/cm^3 at 20°C	O'Neil MJ (2013)	High
Vapor pressure	5.45×10^{-4} mm Hg at 25°C	NLM (2018)	High
Vapor density	Not available		
Water solubility	1.75 mg/L at 25°C	NLM (2018)	High

Property or Endpoint	Value[a]	Reference	Data Quality Rating
Octanol/water partition coefficient (log Kow)	5.9	U.S. EPA (2019f)	High
Henry's Law constant	1.06×10^{-4} atm·m^3/mole at 25°C	U.S. EPA (2012b)	High
Flash point	Not available	-	-
Auto flammability	Not available	-	-
Viscosity	12,914 cP	NLM (2018)	High
Refractive index	1.5342	O'Neil MJ (2013)	High
Dielectric constant	Not available	-	-

[a] Measured unless otherwise noted.
NA = Not applicable

Figure 2-12 displays a summary of the data collected as of June 2020 for eight physical and chemical properties routinely used in TSCA existing chemical risk evaluations. The box and whisker plots for each endpoint illustrate the mean (average, indicated by the blue diamond) and the 10^{th}, 25^{th}, 50^{th} (median), 75^{th}, and 90^{th} percentiles. All individual data points are indicated by black squares, and value preliminarily selected for use in the risk evaluation is overlaid (indicated by the orange circle) to provide context for where it lies within the distribution of the dataset. The number of unique primary data sources is indicated below each box and whisker plot. If multiple sources presented equivalent values and cited the same primary source, only one of those was included in the statistical calculations. As a result, the number of sources listed in Figure 2-12 may differ from the total number of data sources presented in
Figure 2-2. Where no data could be identified through systematic review, text appears to clearly demonstrate the gap for the endpoint.

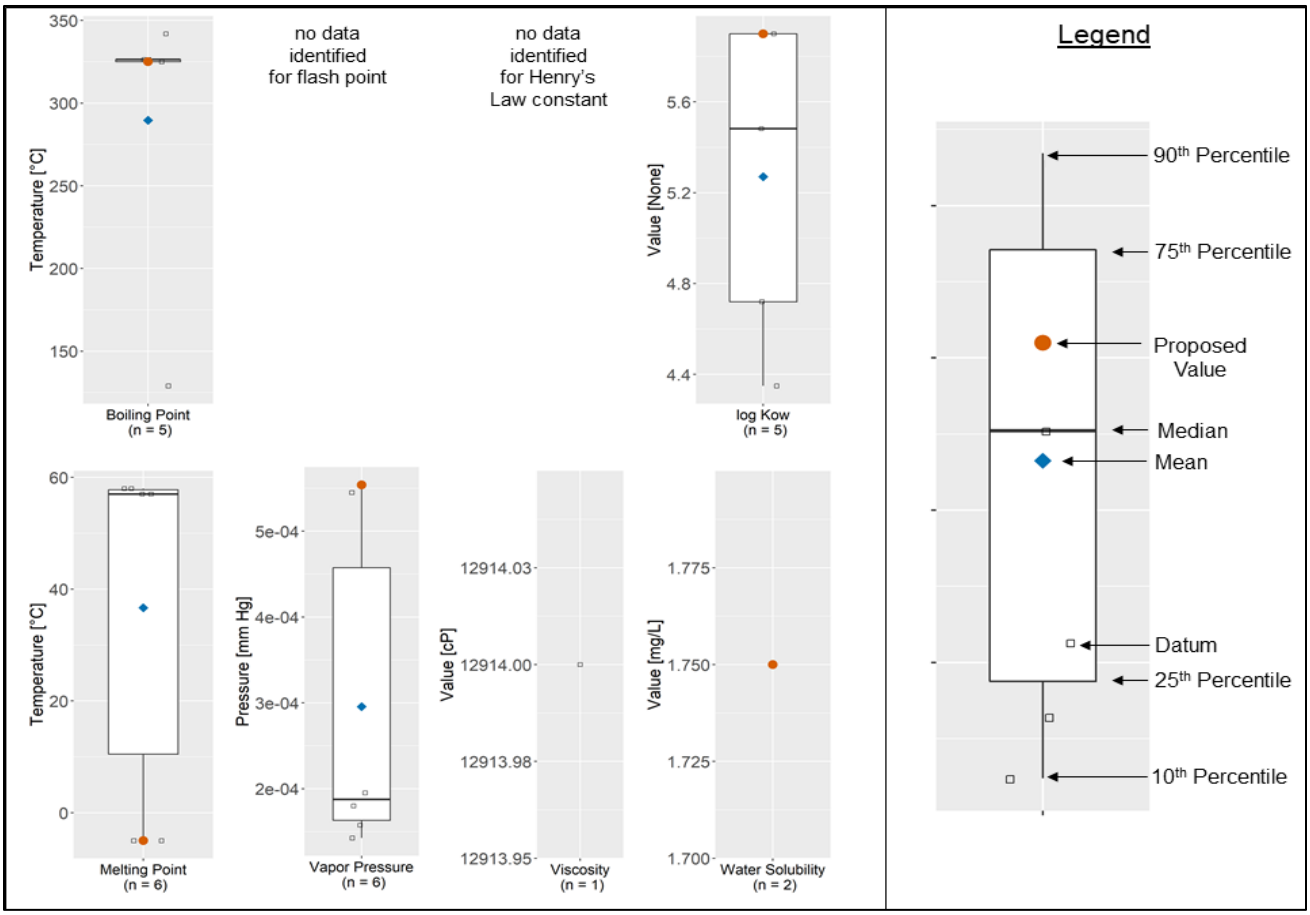


Figure 2-12. Box and Whisker Plots of Reported Physical and Chemical Property Values

2.3.2 Environmental Fate and Transport

Understanding of environmental fate and transport processes assists in the determination of the specific exposure pathways and routes and human and environmental receptors that need to be assessed in the risk evaluation for HHCB. EPA plans to use the environmental fate characteristics described in Appendix C to support the development of the risk evaluation for HHCB. The values for the environmental fate properties may be updated as EPA evaluates and integrates additional information through systematic review methods.

2.3.3 Releases to the Environment

Releases to the environment from conditions of use are a component of potential exposure and may be derived from reported data that are obtained through direct measurement, calculations based on empirical data and/or assumptions and models.

For all conditions of use, EPA plans to review gray literature data sources identified in Appendix A during risk evaluation using systematic review evaluation strategies for environmental releases and occupational exposure data sources. EPA includes TRI data in TSCA existing chemical assessments, but HHCB is not a TRI-listed chemical and thus TRI data are not available. As systematic review continues for HHCB, EPA plans to review gray and peer-reviewed literature to identify potential routes of release of HHCB to the environment. EPA may also reference the Organisation for Economic Co-operation and

Development (OECD) Emission Scenario Document (ESD) *Blending of Fragrance Oils into Commercial and Consumer Products* to evaluate releases from applicable conditions of use.

According to the ESD *Blending of Fragrance Oils into Commercial and Consumer Products*, there may be releases of HHCB from industrial sites to wastewater treatment plants (WWTP), surface water, air, incineration, and landfills (OECD, 2010). Additional releases may occur from the commercial and consumer use of products containing HHCB. HHCB use in cleaning products may result in releases to POTWs. The spraying of air fresheners, use of wax melts, scented candles, or solid air fresheners containing HHCB may release HHCB into indoor air. HHCB formulated into plastic or paper products, may be either incinerated or sent to a landfill.

EPA plans to review these data in conducting the exposure assessment component of the risk evaluation for HHCB.

2.3.4 Environmental Exposures

Manufacturing, processing, distribution, use and disposal of HHCB can result in releases to the environment and exposure to aquatic and terrestrial receptors (biota). Environmental exposures to biota are informed by releases into the environment, overall persistence, degradation, and bioaccumulation, and partitioning across different media. Concentrations of chemical substances in biota provide evidence of exposure. EPA plans to review reasonably available chemical monitoring data for HHCB.

As stated in Section 2.3.3, there may be releases of HHCB from industrial sites to wastewater treatment plants (WWTP), surface water, air, and landfills. Articles that contain HHCB may release HHCB to the environment during use or through recycling and disposal. Similarly, biosolids have been documented to contain HHCB and may release HHCB to the environment when land applied (Kinney et al., 2006; Yang and Metcalfe, 2006).

2.3.5 Occupational Exposures

EPA plans to analyze worker activities where there is a potential for exposure under the conditions of use (manufacturing, processing, industrial/commercial uses, and disposal) described in Section 2.2.1. In addition, EPA plans to evaluate exposure to occupational non-users (ONUs) *i.e.*, workers who do not directly handle the chemical but perform work in an area where the chemical is present. EPA also plans to consider the effect(s) that engineering controls (EC) and/or personal protective equipment (PPE) have on occupational exposure levels as part of the risk evaluation.

Examples of worker activities associated with the conditions of use within the scope of the risk evaluation for HHCB that EPA plans to evaluate include, but are not limited to:

- Unloading and transferring HHCB to and from storage containers to process vessels;
- Handling and disposing of waste containing HHCB;
- Cleaning and maintaining equipment;
- Using HHCB in process equipment (*e.g.*, applicators, process vessels);
- Applying formulations and products containing HHCB onto substrates (*e.g.*, spray applying deodorizing products containing HHCB);
- Sampling chemicals, formulations or products containing HHCB for quality control;
- Repackaging chemicals, formulations or products containing HHCB; and
- Performing other work activities in or near areas where HHCB is used.

HHCB is a liquid with a vapor pressure of 5.45×10^{-4} mm Hg at 25ºC. HHCB's vapor pressure and use as a fragrance chemical indicates the potential for inhalation exposure of workers and ONUs to vapors generated by the liquid at ambient room temperature conditions. Additionally, there is the potential for inhalation exposure to mists generated from use in spraying/aerosol products (*e.g.*, spray air fresheners).

EPA generally does not evaluate occupational exposures through the oral route. Workers and ONUs may inadvertently ingest inhaled particles that deposit in the upper respiratory tract. In addition, workers may transfer chemicals from their hands to their mouths. The frequency and significance of this exposure route are dependent on several factors including the physical and chemical properties of the substance during worker activities, the visibility of the chemicals on the hands while working, workplace training and practices, and personal hygiene that is difficult to predict (Cherrie et al., 2006). EPA plans to consider the relevance of this exposure route on a case-by-case basis, taking into consideration the aforementioned factors and any reasonably available information, and may assess oral exposure for workers for certain COUs and worker activities where warranted. For certain conditions of use of HHCB, EPA plans to consider inhalation exposure to dust/particulates for workers and ONUs. As inhalation exposure to dust/particulates may occur, EPA plans to consider potential exposure for particulates that deposit in the upper respiratory tract from inhalation exposure and may be ingested via the oral route.

Based on the conditions of use, EPA plans to evaluate dermal exposures for workers because workers are expected to have skin contact with solids and liquids. ONUs do not directly handle HHCB; therefore, skin contact with liquid HHCB is not expected for ONUs. EPA plans to analyze dermal exposure for workers and ONUs to mists and dusts that deposit on surfaces.

2.3.6 Consumer Exposures

EPA plans to evaluate consumer uses of HHCB in air care products, cleaning and furnishing care products, laundry and dishwashing products, and paper, plastic, and rubber products.

Consumers using or disposing of these products, and bystanders, may be exposed to HHCB in liquids, vapors, mists and dusts (*i.e.*, powdered detergents) via inhalation. Furthermore, consumers using or disposing of cleaning and furnishing, laundry and dishwashing products may be exposed to HHCB in liquids or mists via skin contact.

The estimated exposure to HHCB on the skin from the use of a combination of all classes of consumer products on a daily basis was calculated by a European Union (EU) assessment to result in a "worst case situation" of 0.85 mg/kg body weight per day (EU, 2008). The inhalation exposure of consumers to HHCB in household cleaning products and air fresheners was estimated as lower, in total 0.0085 mg/kg body weight per day (EU, 2008). The 2008 EU assessment concluded there was no need for further information and/or testing and no need for risk reduction measures beyond those already being applied for consumers (EU, 2008).

EPA plans to analyze inhalation exposures to consumers and bystanders during use of HHCB consumer products. EPA also plans to analyze dermal exposures to consumers during use of HHCB consumer products. However, EPA does not expect dermal exposures to bystanders during consumer use of HHCB.

2.3.7 General Population Exposures

Monitoring data were identified in EPA's data search for HHCB and can be used in the exposure assessment. Relevant and reliable monitoring studies provide information that can be used in an

exposure assessment. Monitoring studies that measure environmental concentrations or concentrations of chemical substances in biota provide evidence of exposure.

The U.S. Geological Survey (USGS) Monitoring Data – National Water Quality Monitoring Council (NWQMC) has identified HHCB in sediment, soil, ground water, and surface water (USGS, 1991a, b, c, d, e). Research suggests moderate-range (regional) atmospheric transport of HHCB may occur, although long-range transport is unlikely (U.S. EPA, 2014). HHCB was identified in filtered and non-filtered drinking water. Measured concentrations within aquatic organisms and birds were also reported (U.S. EPA, 2014).

Releases of HHCB from specific conditions of use, such as consumer and commercial uses, product processing through fragrance compounding, and end-product formulation, disposal, or waste treatment activities may result in general population exposures due to ingestion of contaminated drinking water near industrial processing sites (U.S. EPA, 2014; EU, 2008). Human exposure through ingestion of water and food including fish, root crops, and mother's milk was noted in the 2014 EPA TSCA Workplan Chemicals risk assessment as the main route of exposure to humans (U.S. EPA, 2014). HHCB has been measured in human blood and breast milk (U.S. EPA, 2014). Exposure via inhalation route to the general population was considered negligible, according to the 2014 EPA assessment. Currently, EPA plans to evaluate oral exposure in its assessment of HHCB for the general population. The general population pathways in the scope of this evaluation are described in Sections 2.6.3 and 2.7.2.5.

2.4 Hazards (Effects)

2.4.1 Environmental Hazards

EPA considered reasonably available information (*e.g.*, federal and international government chemical assessments) on HHCB as well as public comments received on the *Proposed Designation of 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-Hexamethylcyclopenta[γ]-2-Benzopyran (HHCB; CASRN 1222-05-5) as a High-Priority Substance for Risk Evaluation* (U.S. EPA, 2019e) and draft scope for HHCB (U.S. EPA, 2020b) to identify potential environmental hazards. During prioritization, EPA identified environmental hazard effects for aquatic and terrestrial organisms.

Since prioritization, EPA applied automated techniques during the data screening phase of systematic review to identify the following potential environmental hazards and related information that may be considered for the risk evaluation (as explained in Appendix A): ADME, cardiovascular, developmental, endocrine, hepatic, mortality, musculoskeletal, neurological, nutritional and metabolic, ocular and sensory, reproductive and skin and connective tissue (Figure 2-10). A summary of references identified during the screening step of systematic review is included in the interactive literature inventory trees (Figure 2-9). As EPA continues to evaluate reasonably available and relevant hazard information identified through systematic review, EPA may update the list of potential hazard effects to be analyzed in the risk evaluation.

2.4.2 Human Health Hazards

EPA considered reasonably available information (*e.g.*, federal and international government chemical assessments) on HHCB as well as through public comments on the *Proposed Designation of 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-Hexamethylcyclopenta[γ]-2-Benzopyran (HHCB; CASRN 1222-05-5) as a High-Priority Substance for Risk Evaluation* (U.S. EPA, 2019e) and draft scope for HHCB (U.S. EPA, 2020b) to identify potential human health hazards. During prioritization, EPA identified potential human health hazards and related information on developmental effects.

Since prioritization, EPA applied automated techniques during the data screening phase of systematic review to identify the following additional potential human health hazards and related information that may be considered for the risk evaluation (as explained in Appendix A): endocrine, mortality, musculoskeletal, reproductive and skin and connective tissue (Figure 2-10). A summary of references identified during the screening step of systematic review is included in the interactive literature inventory trees (Figure 2-9). As EPA continues to evaluate reasonably available and relevant hazard information identified through systematic review, EPA may update the list of potential hazard effects to be analyzed in the risk evaluation.

2.5 Potentially Exposed or Susceptible Subpopulations

TSCA§ 6(b)(4) requires EPA to determine whether a chemical substance presents an unreasonable risk to "a potentially exposed or susceptible subpopulation identified as relevant to the risk evaluation." TSCA §3(12) states that "the term 'potentially exposed or susceptible subpopulation' means a group of individuals within the general population identified by the Administrator who, due to either greater susceptibility or greater exposure, may be at greater risk than the general population of adverse health effects from exposure to a chemical substance or mixture, such as infants, children, pregnant women, workers, or the elderly." General population is "the total of individuals inhabiting an area or making up a whole group" and refers here to the U.S. general population (U.S. EPA, 2011a).

EPA identified the following PESS based on CDR information, public comments received on the draft scope for HHCB, and studies reporting developmental and reproductive effects: children, women of reproductive age (*e.g.*, pregnant women), workers, including ONUs; and consumers, including users and bystanders (U.S. EPA, 2019b). In addition, preliminary information indicates that HHCB may bioaccumulate in fish (Appendix C); thus, populations with elevated fish ingestion are considered potentially exposed or susceptible. EPA plans to evaluate these PESS in the risk evaluation. Following further evaluation of the reasonably available information, EPA may evaluate PESS in the general population as they relate to fence line communities.

In developing exposure scenarios, EPA plans to analyze reasonably available data to ascertain whether some human receptor groups may be exposed via exposure pathways that may be distinct to a particular subpopulation or life stage (*e.g.*, children's crawling, mouthing or hand-to-mouth behaviors, ingestion of breast milk) and whether some human receptor groups may have higher exposure via identified pathways of exposure due to unique characteristics (*e.g.*, activities, duration or location of exposure) when compared with the general population (U.S. EPA, 2006b). Likewise, EPA plans to evaluate reasonably available human health hazard information to ascertain whether some human receptor groups may have greater susceptibility than the general population to the chemical's hazard(s). Based on these analyses, EPA may update the list of PESS in the risk evaluation.

2.6 Conceptual Models

In this section, EPA presents the conceptual models describing the identified exposures (pathways and routes), receptors, and hazards associated with the conditions of use of HHCB. Pathways and routes of exposure associated with workers and ONUs are described in Section 2.6.1, and pathways and routes of exposure associated with consumers are described in Section 2.6.2. Pathways and routes of exposure associated with environmental releases and wastes are discussed and depicted in the conceptual model shown in Section 2.6.3.

2.6.1 Conceptual Model for Industrial and Commercial Activities and Uses

Figure 2-13 illustrates the conceptual model for the pathways of exposure from industrial and commercial activities and uses of HHCB that EPA plans to include in the risk evaluation. There are exposures to workers and ONUs via inhalation routes and exposures to workers via dermal routes for all conditions of use identified in this scoping document. The conceptual model includes potential inhalation exposures to HHCB through vapor, mists, and dusts, and dermal exposures through contact with solid and liquid HHCB. In addition to the pathways illustrated in the figure, EPA plans to evaluate activities resulting in exposures associated with distribution in commerce (*e.g.* loading, unloading) throughout the various lifecycle stages and conditions of use (*e.g.* manufacturing, processing, industrial use, commercial use, disposal) rather than a single distribution scenario.

For each condition of use identified in Table 2-2, a determination was made as to whether or not EPA plans to evaluate each combination of exposure pathway, route, and receptor in the risk evaluation. The results of that analysis along with the supporting rationale are presented in Appendix F.

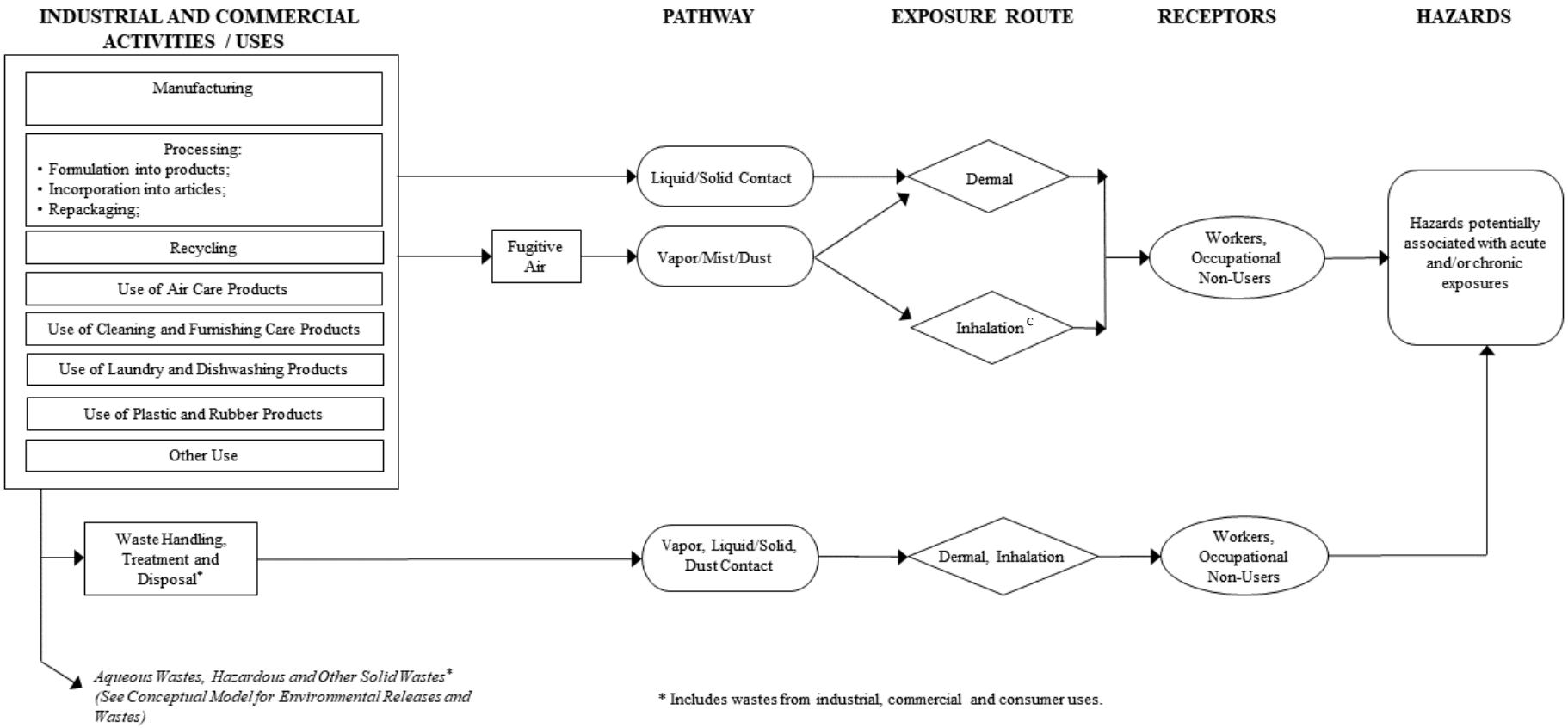


Figure 2-13. HHCB Conceptual Model for Industrial and Commercial Activities and Uses: Worker and ONU Exposures and Hazards
The conceptual model presents the exposure pathways, exposure routes and hazards to human receptors from industrial and commercial activities and uses of HHCB.
a) Receptors include PESS (see Section 2.5).
b) When data and information are available to support the analysis, EPA also considers the effect that EC and/or PPE have on occupational exposure level.
c) Inhalation exposure route includes potential for the oral route via ingestion of inhaled dust/particulates.

2.6.2 Conceptual Model for Consumer Activities and Uses

The conceptual model in Figure 2-14 presents the exposure pathways, exposure routes and hazards to human receptors from consumer activities and uses of HHCB that EPA plans to include in the risk evaluation. Inhalation is expected to be the primary route of exposure for consumers and plans to evaluate inhalation exposures to HHCB vapors, mists, and dusts for consumers and bystanders. EPA plans to evaluate dermal exposures via mists and direct contact to HHCB during the consumer uses of the product types listed in Figure 2-14 . Oral exposures to HHCB during consumer uses are expected to be negligible. As a result, oral ingestion of HHCB will not be evaluated for consumers. In addition, since bystanders are not expected to have significant direct dermal or oral contact to HHCB, these pathways will not be evaluated for bystanders. The supporting rationale for consumer pathways considered for HHCB are included in Appendix G.

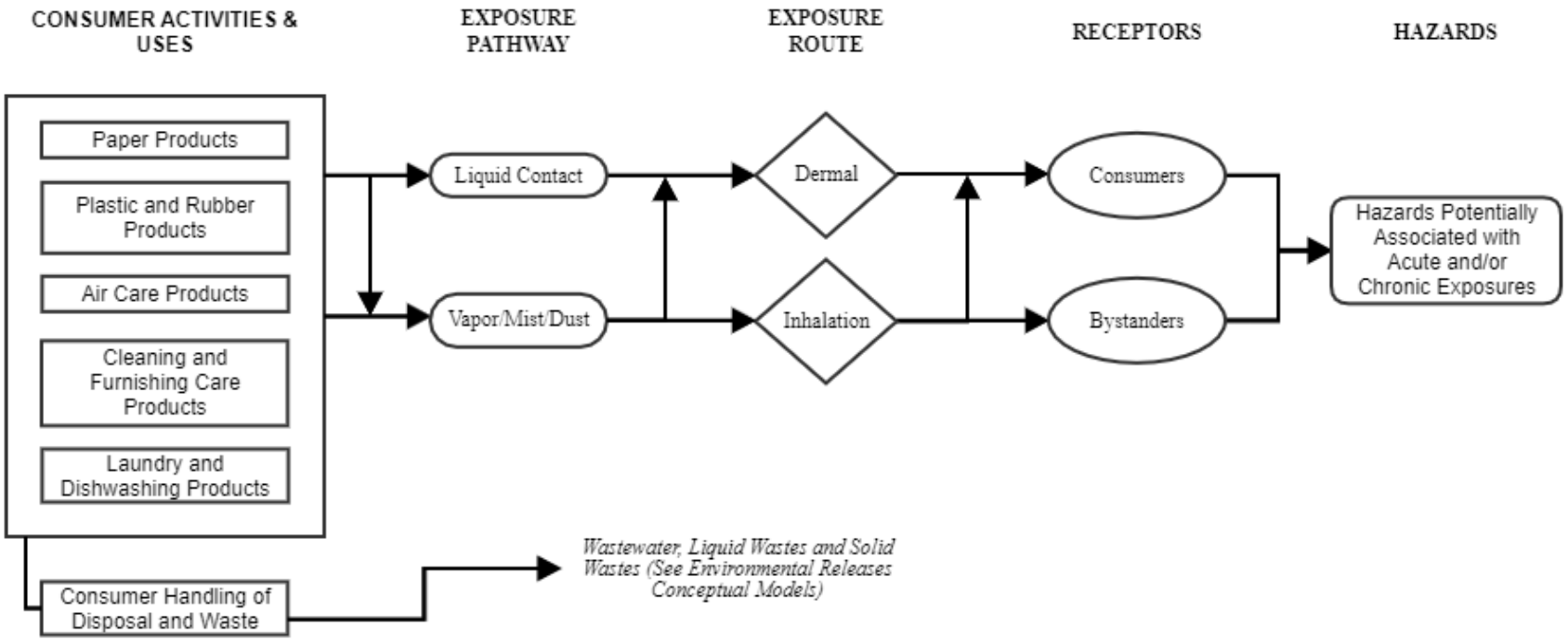


Figure 2-14. HHCB Conceptual Model for Consumer Activities and Uses: Consumer Exposures and Hazards
The conceptual model presents the exposure pathways, exposure routes and hazards to human receptors from consumer activities and uses of HHCB.
a) Receptors include PESS (see Section 2.5).

2.6.3 Conceptual Model for Environmental Releases and Wastes: Potential Exposures and Hazards

In this section, EPA presents the conceptual models describing the identified exposures (pathways and routes from environmental releases and wastes) and hazards to general population and environmental receptors and hazards associated with the conditions of use of HHCB within the scope of the risk evaluation.

The conceptual model in Figure 2-15 presents the potential exposure pathways, exposure routes and hazards to general population and environmental receptors from releases and waste streams associated with the industrial, commercial, and consumer uses of HHCB within the scope of the risk evaluation. EPA plans to evaluate exposures to receptors (*e.g.*, general population, aquatic, terrestrial species) that may occur from releases to air, drinking water, ground water, and land, including biosolids and soil. Some aquatic species may be exposed to HHCB by consuming sediments and swimming in water bodies in which HHCB is found. Some terrestrial species may be exposed to HHCB via air and soil found in their natural habitats. Furthermore, the general population may receive oral exposure to HHCB via fish ingestion and drinking water. The general population may also receive dermal and oral exposures to HHCB through recreational actives such as swimming in surface water bodies. In addition, the-general population may receive inhalation exposures to HHCB from ambient air and through vapor emissions from soil or recycled wastes. The supporting basis for general population and environmental pathways considered for HHCB are included in Appendix H.

In its TSCA Section 6(b) risk evaluations, EPA is coordinating action on certain exposure pathways and risks falling under the jurisdiction of other EPA-administered statutes or regulatory programs. More specifically, EPA is exercising its TSCA authorities to tailor the scope of its risk evaluations, rather than focusing on environmental exposure pathways addressed under other EPA-administered statutes or regulatory programs or risks that could be eliminated or reduced to a sufficient extent by actions taken under other EPA-administered laws. However, no other regulatory programs cover the environmental release and waste pathways for HHCB. The scope of the HHCB risk evaluation will include all exposure pathways relevant to the COUs described in Section 2.2.

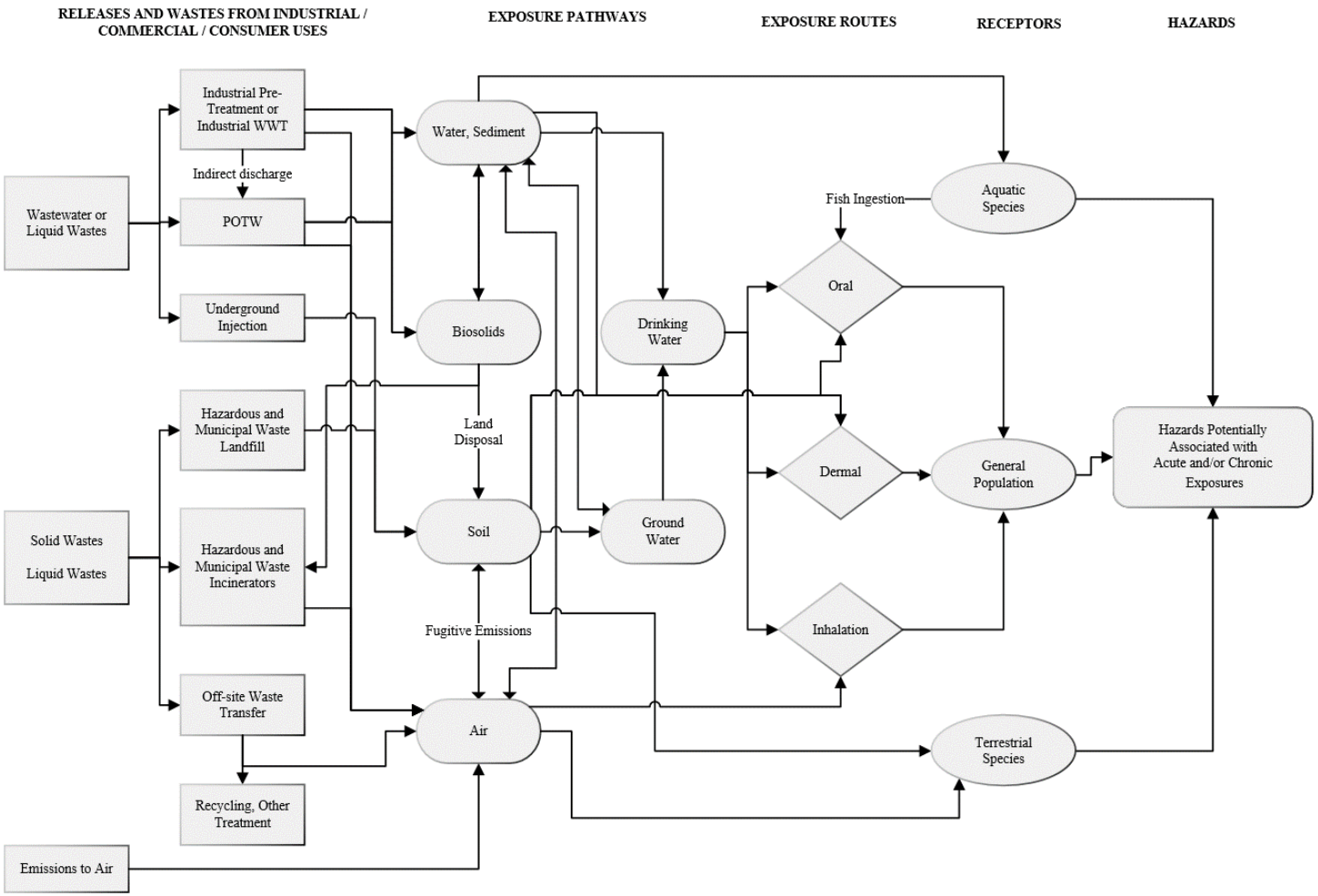


Figure 2-15. HHCB Conceptual Model for Environmental Releases and Wastes: Environmental Exposures and Hazards

The conceptual model presents the exposure pathways, exposure routes and hazards to human and environmental receptors from releases and wastes from industrial, commercial, and consumer uses of HHCB that EPA plans to consider in the risk evaluation.

a) Industrial wastewater or liquid wastes may be treated on-site and then released to surface water (direct discharge), or pre-treated and released to Publicly Owned Treatment Works (POTW) (indirect discharge). For consumer uses, such wastes may be released directly to POTW. Drinking water will undergo further treatment in drinking water treatment plant. Ground water may also be a source of drinking water. Inhalation from drinking water may occur via showering

b) Receptors include PESS (See Section 2.5).

2.7 Analysis Plan

The analysis plan is based on EPA's knowledge of HHCB resulting from the full-text screening of reasonably available information as described in Section 2.1. EPA encourages submission of additional existing data, such as full study reports or workplace monitoring from industry sources, that may be relevant to EPA's evaluation of conditions of use, exposures, hazards and PESS during risk evaluation. As discussed in the *Application of Systematic Review in TSCA Risk Evaluations* document (U.S. EPA, 2018), targeted supplemental searches during the analysis phase may be necessary to identify additional information (*e.g.*, commercial mixtures) for the risk evaluation of HHCB. For any additional data needs identified during the risk evaluation, EPA may use the Agency's TSCA authorities under Sections 4, 8 or 11, as appropriate.

2.7.1 Physical and Chemical Properties and Environmental Fate

EPA plans to analyze the physical and chemical properties and environmental fate and transport of HHCB as follows:

1) **Review reasonably available measured or estimated physical and chemical property and environmental fate endpoint data collected using systematic review procedures and, where reasonably available, environmental assessments conducted by other regulatory agencies.** EPA plans to evaluate data and information collected through the systematic review methods and public comments about the physical and chemical properties (Appendix B) and fate endpoints (Appendix C), some of which appeared in the *Proposed Designation of 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-Hexamethylcyclopenta[γ]-2-Benzopyran (HHCB; CASRN 1222-05-5) as a High-Priority Substance for Risk Evaluation* (U.S. EPA, 2019e). All sources cited in EPA's analysis will be evaluated according to the procedures and metrics described in *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018). Where the systematic review process does not identify experimentally measured chemical property values of sufficiently high quality, testing will be requested under the TSCA Section 4 authority, or values will be estimated using chemical parameter estimation models as appropriate. Model-estimated fate properties will be reviewed for applicability and quality.

2) **Using measured data and/or modeling, determine the influence of physical and chemical properties and environmental fate endpoints (*e.g.*, persistence, bioaccumulation, partitioning, transport) on exposure pathways and routes of exposure to human and environmental receptors.**
Measured data and, where necessary, model predictions of physical and chemical properties and environmental fate endpoints will be used to characterize the persistence and movement of HHCB within and across environmental media. The fate endpoints of interest include volatilization, sorption to organic matter in soil and sediments, water solubility, aqueous and atmospheric photolysis rates, aerobic and anaerobic biodegradation rates, and potential bioconcentration and bioaccumulation. These endpoints will be used in exposure calculations.

3) **Conduct a weight of scientific evidence evaluation of physical and chemical and environmental fate data, including qualitative and quantitative sources of information.** During risk evaluation, EPA plans to evaluate and integrate the physical and chemical and environmental fate evidence identified in the literature inventory using methods described in the *Draft Systematic Review Protocol Supporting the TSCA Risk Evaluations* (EPA document # 740-D-20-031).

2.7.2 Exposure

EPA plans to analyze exposure levels for indoor air, ambient air, surface water, drinking water, sediment, soil, ground water, aquatic biota, and terrestrial biota associated to exposure to HHCB. Based on its physical and chemical properties, expected sources, and transport and transformation within the outdoor and indoor environment, HHCB is more likely to be present in some of these media and less likely to be present in others. EPA has not yet determined the exposure levels in these media. Exposure level(s) can be characterized through a combination of reasonably available monitoring data and estimated exposure levels from modeling approaches. Exposure scenarios are combinations of sources (uses), exposure pathways, and exposed receptors. Draft exposure scenarios corresponding to various conditions of use for HHCB are presented in Appendix F, Appendix G, and Appendix H. EPA plans to analyze scenario-specific exposures.

2.7.2.1 Environmental Releases

EPA plans to analyze releases to environmental media as follows:

1) **Review reasonably available published literature and other reasonably available information on processes and activities associated with the conditions of use to analyze the types of releases and wastes generated.**
   EPA has reviewed some key data sources containing information on processes and activities resulting in releases, and the information found is described in Appendix E. EPA plans to continue to review data sources identified. Potential sources of environmental release data are summarized in Table 2-4.

   Table 2-4. Categories and Sources of Environmental Release Data

U.S. EPA Generic Scenarios
U.S. EPA/OPPT 2014 HHCB Risk Assessment
OECD Emission Scenario Documents
EU Risk Assessment Reports

2) **Review reasonably available chemical-specific release data, including measured or estimated release data (*e.g.*, data from risk assessments by other environmental agencies).**
   EPA has reviewed some key release data sources as summarized in Section 2.3.3. EPA plans to consider additional reasonably available information and will evaluate it during development of the risk evaluation. EPA plans to match identified data to applicable conditions of use and identify data gaps where no data are found for specific conditions of use. EPA plans to attempt to address data gaps identified as described in #3 and #4 below by considering potential surrogate data and models.

   Additionally, for conditions of use where no measured data on releases are reasonably available, EPA may use a variety of methods including release estimation approaches and assumptions in the Chemical Screening Tool for Exposures and Engineering Releases (ChemSTEER) (U.S. EPA, 2015a).

3) **Review reasonably available measured or estimated release data for surrogate chemicals that have similar uses and physical properties.**
   EPA plans to review literature sources identified and if surrogate data are found, EPA plans to match these data to applicable conditions of use for potentially filling data gaps.

4) **Review reasonably available data that may be used in developing, adapting or applying exposure models to the particular risk evaluation.**
This item will be performed after completion of #2 and #3 above. EPA plans to evaluate relevant data to determine whether the data can be used to develop, adapt or apply models for specific conditions of use (and corresponding release scenarios). EPA has identified information from various EPA statutes and sources (including, for example, regulatory limits, reporting thresholds or disposal requirements) that may be relevant to consider for release estimation and environmental exposures. EPA plans to consider relevant regulatory requirements in estimating releases during risk evaluation.

5) **Review and determine applicability of OECD Emission Scenario Documents (ESDs) and EPA Generic Scenarios to estimation of environmental releases.**
EPA has identified potentially relevant OECD Emission Scenario Documents (ESDs) and EPA Generic Scenarios (GS) that correspond to some conditions of use; for example, the 2010 ESD on The Blending of Fragrance Oils into Commercial and Consumer Products (OECD, 2010) may be useful as well as the ESD on Plastic Additives (OECD, 2009b) and the complementing document on Plastic Additives During the Use of End Products (OECD, 2019). EPA plans to critically review these generic scenarios and ESDs to determine their applicability to the conditions of use assessed.

EPA Generic Scenarios are available at the following: https://www.epa.gov/tsca-screening-tools/chemsteer-chemical-screening-tool-exposures-and-environmental-releases.

OECD Emission Scenario Documents are available at the following: http://www.oecd.org/chemicalsafety/risk-assessment/emissionscenariodocuments.htm

If ESDs and GSs are not available, other methods may be considered. EPA may also perform supplemental targeted searches of peer-reviewed or gray literature for applicable models and associated parameters that EPA may use to estimate releases for certain conditions of use. Additionally, for conditions of use where no measured data on releases are available, EPA may use a variety of methods including the application of default assumptions such as standard loss fractions associated with drum cleaning (3%) or single process vessel cleanout (1%).

6) **Map or group each condition of use to a release assessment scenario(s).**
EPA has completed initial mapping of release scenarios to relevant conditions of use as shown in Appendix F. EPA plans to refine the mapping/grouping of release scenarios based on factors (*e.g.*, process equipment and handling, magnitude of production volume used, and exposure/release sources) corresponding to conditions of use using reasonably available information. EPA may perform supplemental targeted searches of peer-reviewed or gray literature to better understand certain conditions of use to further develop release scenarios.

7) **Evaluate the weight of the scientific evidence of environmental release data.**
During risk evaluation, EPA plans to evaluate and integrate the environmental release evidence identified in the literature inventory using the methods described in the *Application of Systematic Review in TSCA Risk Evaluation* (U.S. EPA, 2018). EPA plans to integrate the data using

systematic review methods to assemble the relevant data, evaluate the data for quality and relevance, including strengths and limitations, followed by synthesis and integration of the evidence.

2.7.2.2 Environmental Exposures

EPA plans to analyze the following in developing its environmental exposure assessment of HHCB:

1) **Review reasonably available environmental and biological monitoring data for all media relevant to environmental exposure.**
   For HHCB, environmental media which EPA plans to analyze are sediment, biosolids, soil, ambient air and surface water. The environmental exposure pathways which have been identified in the literature include aquatic and terrestrial.

2) **Review reasonably available information on releases to determine how modeled estimates of concentrations near industrial point sources compare with reasonably available monitoring data.**
   EPA plans to analyze and consider reasonably available environmental exposure models that meet the scientific standards under TSCA Section 26(h) and that estimate surface water, sediment, and soil concentrations alongside reasonably available surface water, sediment, and soil monitoring data to characterize environmental exposures. Modeling approaches to estimate surface water concentrations, sediment concentrations and soil concentrations will include the following inputs: direct release into surface water, sediment, or soil, indirect release into surface water, sediment, or soil (*i.e.*, air deposition), fate and transport (partitioning within media) and characteristics of the environment (*e.g.*, river flow, volume of lake, meteorological data).

3) **Review and characterize reasonably available biomonitoring data for vegetation, invertebrates, fish, non-fish vertebrates (*i.e.*, amphibians, reptiles, mammals). Consider whether these data could be used to compare with comparable species or taxa-specific toxicological benchmarks.**
   Predatory bird species that consume fish with elevated levels of HHCB will be analyzed. If species-specific biomonitoring data matches toxicity studies, direct comparisons can be made. EPA plans to also consider refining data for other species by using body weight of the birds, fish ingestion rate of birds, and typical fish species consumed.

4) **Determine applicability of existing additional contextualizing information for any monitored data or modeled estimates during risk evaluation.**
   There have been changes to use patterns of HHCB over the last few years. Review and characterize monitoring data or modeled estimates to determine how representative they are of applicable use patterns.

   Any studies which relate levels of HHCB in the environment or biota with specific sources or groups of sources will be evaluated.

5) **Group each condition(s) of use to the environmental assessment scenario(s).**
   EPA plans to refine and finalize exposure scenarios for environmental receptors by considering combinations of sources (use descriptors), exposure pathways including routes, and populations exposed. For HHCB, the following are noteworthy considerations in constructing exposure scenarios for environmental receptors:

- Estimates of surface water concentrations, sediment concentrations and soil concentrations near industrial point sources based on reasonably available monitoring data;
- Modeling inputs related to release into the media of interest, fate and transport, and characteristics of the environment;
- Reasonably available biomonitoring data which could be used to compare with species or taxa-specific toxicological benchmarks;
- Applicability of existing additional contextualizing information for any monitored data or modeled estimates during risk evaluation (review and characterize the spatial and temporal variability, to the extent that data are reasonably available, and characterize exposed aquatic and terrestrial populations); and
- Weight of the scientific evidence of environmental occurrence data and modeled estimates.

6) **Evaluate the weight of the scientific evidence of environmental occurrence data and modeled estimates.**
During risk evaluation, EPA plans to evaluate and integrate the exposure evidence identified in the literature inventory using the methods described in the *Application of Systematic Review in TSCA Risk Evaluation* (U.S. EPA, 2018).

2.7.2.3 Occupational Exposures

EPA plans to analyze both worker and ONU exposures as follows:

1) **Review reasonably available exposure monitoring data for specific condition(s) of use.**
EPA plans to review exposure monitoring data found in published literature (including both personal exposure monitoring data (direct exposures) and area monitoring data (indirect exposures)). EPA has identified reasonably available monitoring data collected by the Occupational Safety and Health Administration (OSHA) and National Institute for Occupational Safety and Health (NIOSH) and neither collected data for HHCB exposures. The most recent submissions to CDR for HHCB will be used to identify manufacturing and processing information for HHCB where occupational exposure may occur. CDR data was also used to identify uses of HHCB that would lead to occupational exposures.

   EPA plans to continue to review data sources identified through systematic review for HHCB using systematic review evaluation strategies for occupational exposure data sources.

2) **Review reasonably available exposure data for surrogate chemicals that have uses, volatility and chemical and physical properties similar to HHCB.**
EPA plans to review literature sources identified and if surrogate data are found, these data will be matched to applicable conditions of use for potentially filling data gaps. For several conditions of use (*e.g.*, air care products, cleaners, and laundry products), EPA may consider other similar fragrances that share the same conditions of use as possible surrogates for HHCB.

3) **For conditions of use where data are limited or not reasonably available, review existing exposure models that may be applicable in estimating exposure levels.**
EPA has identified Emission Scenario Documents (ESDs) from the OECD. For example, the ESD on The Blending of Fragrance Oils into Commercial and Consumer Products (OECD, 2010) may be used to estimate occupational exposures as well as the ESD on Plastic Additives

(OECD, 2009b) and the complementing document on Plastic Additives During the Use of End Products (OECD, 2019). EPA plans to critically review all generic scenarios and ESDs to determine their applicability to the conditions of use assessed. EPA may conduct industry outreach efforts or perform supplemental, targeted searches of peer-reviewed or gray literature to understand those conditions of use, which may inform identification of exposure scenarios.

EPA plans to consider inhalation exposure to vapor and mist models in the ChemSTEER Tool that are routinely used for assessing new chemicals. EPA may also need to perform targeted supplemental searches to identify applicable models that EPA could use to estimate exposures for certain conditions of use (U.S. EPA, 2015a).

4) **Review reasonably available data that may be used in developing, adapting or applying exposure models to a particular risk evaluation scenario.**
This will be performed after #2 and #3 are completed, and based on information developed from #2 and #3, EPA plans to evaluate relevant data to determine whether the data can be used to develop, adapt, or apply models for specific conditions of use (and corresponding exposure scenarios). EPA may utilize existing, peer-reviewed exposure models developed by EPA, other government agencies, or reasonably available in the scientific literature, or EPA may elect to develop additional models to assess specific condition(s) of use. Inhalation exposure models may be simple box models or two-zone (near-field/far-field) models. In two-zone models, the near-field exposure represents potential inhalation exposures to workers, and the far-field exposure represents potential inhalation exposures to ONUs.

5) **Consider and incorporate applicable EC and/or PPE into exposure scenarios.**
OSHA requires employers utilize the hierarchy of controls to address hazardous exposures in the workplace. The hierarchy of controls strategy outlines, in descending order of priority, the use of elimination, substitution, engineering controls, administrative controls, and lastly personal protective equipment (PPE). EPA plans to review potentially relevant data sources on EC and PPE to determine their applicability and incorporation into exposure scenarios during risk evaluation. EPA plans to assess worker exposure pre- and post-implementation of EC, using reasonably available information on control technologies and control effectiveness. For example, EPA may assess worker exposure in industrial use scenarios before and after implementation of local exhaust ventilation.

6) **Map or group each condition of use to occupational exposure assessment scenario(s).**
EPA has identified occupational exposure scenarios and mapped them to relevant conditions of use (see Appendix F). As presented in the fourth column in Table_Apx F-1, EPA has completed an initial mapping of exposure scenarios to conditions of use. EPA plans to refine mapping or grouping of occupational exposure scenarios based on factors (*e.g.*, process equipment and handling, magnitude of production volume used, and exposure/release sources) corresponding to conditions of use as additional information is identified during risk evaluation. EPA may perform supplemental targeted searches of peer-reviewed or gray literature to better understand certain conditions of use to further develop exposure scenarios.

7) **Evaluate the weight of the scientific evidence of occupational exposure data, which may include qualitative and quantitative sources of information.**
During risk evaluation, EPA plans to evaluate and integrate the exposure evidence identified in

the literature using the methods described in the *Application of Systematic Review in TSCA Risk Evaluation* (U.S. EPA, 2018). EPA plans to rely on the weight of the scientific evidence when evaluating and integrating occupational data. EPA plans to integrate the data using systematic review methods to assemble the relevant data, evaluate the data for quality and relevance, including strengths and limitations, followed by synthesis and integration of the evidence.

2.7.2.4 Consumer Exposures

EPA plans to analyze both consumers using a consumer product and bystanders associated with the consumer using the product as follows:

1) **Group each condition of use to consumer exposure assessment scenario(s).**
   Refine and finalize exposure scenarios for consumers by considering combinations of sources (ongoing consumer uses), exposure pathways including routes, and exposed populations.

   For HHCB, the following are noteworthy considerations in constructing consumer exposure scenarios:

   - Conditions of use
   - Duration, frequency and magnitude of exposure
   - Weight fraction of chemical in products
   - Amount of chemical used

2) **Evaluate the potential of indoor exposure pathways based on reasonably available data.**
   Based on the physical and chemical properties of HHCB and the consumer uses identified, inhalation of vapors, mists, and dusts and liquid dermal contact are expected to be important indoor exposure pathways for consumers. EPA plans to review all reasonably available information in developing the consumer exposure scenarios and evaluating the exposure pathways in indoor environments.

3) **Review existing indoor exposure models that may be applicable in estimating indoor air exposures.**
   Indoor exposure models that estimate emissions from use of consumer products are available. These models generally consider p-chem properties (*e.g.*, vapor pressure, molecular weight), product specific properties (*e.g.*, weight fraction of the chemical in the product), use patterns (*e.g.*, duration and frequency of use), user environment (*e.g.*, room of use, ventilation rates), and receptor characteristics (*e.g.*, exposure factors, activity patterns). The OPPT's Consumer Exposure Model (CEM) and other similar models can be used to estimate indoor air exposures from consumer products.

   Models that estimate emission and migration of semi-volatile organic compounds (SVOCs) into the indoor environment models generally consider indoor fate and transport properties such as mass transfer as informed by the gas-phase mass transfer coefficient, the solid-phase diffusion coefficient and the material-air partition coefficient. These properties vary based on physical and chemical properties and properties of the material. The OPPT's Indoor Environmental Concentrations in Buildings with Conditioned and Unconditioned Zones (IECCU) model and other similar models can be used to estimate indoor air and dust exposures from indoor sources.

4) **Review reasonably available empirical data that may be used in developing, adapting or applying exposure models to a particular risk evaluation scenario. For example, existing**

models developed for a chemical assessment may be applicable to another chemical assessment if model parameter data are reasonably available.
To the extent other organizations have already modeled a HHCB consumer exposure scenario that is relevant to OPPT's evaluation, EPA plans to evaluate those modeled estimates. In addition, if other chemicals similar to HHCB have been modeled for similar uses, those modeled estimates will also be evaluated. The underlying parameters and assumptions of the models will also be evaluated.

5) **Review reasonably available consumer product-specific sources to determine how those exposure estimates compare with each other and with indoor monitoring data reporting HHCB in specific media (*e.g.*, dust or indoor air).**
The availability of HHCB concentration for various conditions of use will be evaluated. This data provides the source term for any subsequent indoor modeling. EPA plans to analyze source attribution between overall indoor air and dust levels and various indoor sources.

6) **Review reasonably available population- or subpopulation-specific exposure factors and activity patterns to determine if PESS need to be further refined.**
For HHCB, EPA plans to evaluate exposure scenarios that involve PESS and plans to consider age-specific behaviors, activity patterns and exposure factors unique to those subpopulations. For some exposure scenarios related to consumer uses, EPA plans to consider whether exposures for adults may differ from those of children due to different activities (*e.g.*, children may mouth certain products) or exposure factors (*e.g.*, inhalation rates).

7) **Evaluate the weight of the scientific evidence of consumer exposure estimates based on different approaches.**
EPA plans to rely on the weight of the scientific evidence when evaluating and integrating data related to consumer exposure. The weight of the scientific evidence may include qualitative and quantitative sources of information. EPA plans to integrate the data using systematic review methods to assemble the relevant data, evaluate the data for quality and relevance, including strengths and limitations, followed by synthesis and integration of the evidence.

2.7.2.5 General Population

EPA plans to analyze general population exposures as follows:

1) **Refine and finalize exposure scenarios for the general population by considering sources and conditions of use, exposure pathways, and routes.**
For HHCB, the following are considerations in constructing exposure scenarios for the general population:

- Reviewing reasonably available environmental and biological monitoring data for media to which general population exposures are expected.
- For exposure pathways where data are not reasonably available, reviewing existing exposure modeling approaches that may be applicable in estimating exposure levels.
- Reviewing reasonably available data that may be used in developing, adapting or applying exposure models to the particular risk evaluation; for example, existing models developed for a chemical assessment may be applicable to another chemical assessment if model parameter data are reasonably available and relevant.

- Reviewing reasonably available information on releases to determine how modeled estimates of concentrations near industrial point sources compare with reasonably available monitoring data.
- Reviewing reasonably available population- or subpopulation-specific exposure factors and activity patterns to determine if PESS need be further defined.
- Evaluating the weight of the scientific evidence of general population exposure data; and
- Map or group each condition of use to general population exposure assessment scenario(s).

EPA plans to evaluate a variety of data types to determine which types are most appropriate when quantifying exposure scenarios. Environmental monitoring data, biomonitoring data, modeled estimates, experimental data, epidemiological data, and survey-based data can all be used to inform exposure scenarios. EPA anticipates that there will be a range in the potential exposures associated with the exposure scenarios identified in Section 2.6.

After refining and finalizing exposure scenarios, EPA plans to quantify concentrations and/or doses. The number of scenarios will depend on the conditions of use, exposure pathways, and receptors. The number of scenarios is also dependent upon the reasonably available data and approaches to quantify scenarios. When quantifying exposure scenarios, EPA plans to use a tiered approach. First-tier analysis may be qualitative, semi-quantitative, or quantitative. The results of first tier analyses inform whether scenarios require more refined analysis. Refined analyses will be iterative and include careful consideration of variability and uncertainty.

2) **For exposure pathways where empirical data is not reasonably available, review existing exposure models that may be applicable in estimating exposure levels.**
For HHCB, media where exposure models will be considered for general population exposure include models that estimate ambient air concentrations, surface water concentrations, drinking water, sediment concentrations, soil concentrations, and uptake from aquatic and terrestrial environments into edible aquatic and terrestrial organisms.

3) **Review reasonably available exposure modeled estimates. For example, existing models developed for a previous HHCB chemical assessment may be applicable to EPA's assessment. In addition, another chemical's assessment may also be applicable if model parameter data are reasonably available.**
To the extent other organizations have already modeled HHCB general population exposure scenario that is relevant to the OPPT's assessment, EPA plans to evaluate those modeled estimates. In addition, if modeled estimates for other chemicals with similar physical and chemical properties and similar uses are available, those modeled estimates will also be evaluated. The underlying parameters and assumptions of the models will also be evaluated.

4) **Review reasonably available information on releases to determine how modeled estimates of concentrations near industrial point sources compare with reasonably available monitoring data.**
The expected releases from industrial facilities are changing over time. Any modeled concentrations based on recent release estimates will be carefully compared with reasonably available monitoring data to determine representativeness.

5) **Review reasonably available information about population- or subpopulation-specific exposure factors and activity patterns to determine if PESS need to be further defined (*e.g.*, early life and/or puberty as a potential critical window of exposure).**
For HHCB, exposure scenarios that involve PESS will consider age-specific behaviors, activity patterns, and exposure factors unique to those subpopulations. For example, children will have different intake rates for soil, and diet than adults.

6) **Evaluate the weight of the scientific evidence of general population exposure estimates based on different approaches.**
During the risk evaluation, EPA plans to evaluate and integrate the exposure evidence identified in the literature inventory using the methods described in the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018).

2.7.3 Hazards (Effects)

2.7.3.1 Environmental Hazards

EPA plans to conduct an environmental hazard assessment of HHCB as follows:

1) **Review reasonably available environmental hazard data, including data from alternative test methods (*e.g.*, computational toxicology and bioinformatics; high-throughput screening methods; data on categories and read-across; *in vitro* studies).**
EPA plans to analyze the hazards of HHCB to aquatic and terrestrial organisms, including plants, invertebrates (*e.g.*, insects, arachnids, mollusks, crustaceans), and vertebrates (*e.g.*, mammals, birds, amphibians, fish, reptiles) across exposure durations and conditions if potential environmental hazards are identified through systematic review results and public comments. Additional types of environmental hazard information will also be considered (*e.g.*, analogue and read-across data) when characterizing the potential hazards of HHCB to aquatic and terrestrial organisms.

   EPA plans to evaluate environmental hazard data using the evaluation strategies laid out in the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018). The study evaluation results will be documented in the risk evaluation phase and data from acceptable studies will be extracted and integrated in the risk evaluation process.

   Mechanistic data may include analyses of alternative test data such as novel *in vitro* test methods and high throughput screening. The association between acute and chronic exposure scenarios to the agent and each health outcome will also be integrated. Study results will be extracted and presented in evidence tables or another appropriate format by organ/system.

2) **Derive hazard thresholds for aquatic and terrestrial organisms.**
Depending on the robustness of the evaluated data for a particular organism or taxa (*e.g.*, aquatic invertebrates), environmental hazard values (*e.g.*, EC_x, LC_x, NOEC, LOEC, *etc*.) may be derived and used to further understand the hazard characteristics of HHCB to aquatic and terrestrial species. Identified environmental hazard thresholds may be used to derive concentrations of concern (COC), based on endpoints that may affect populations of organisms or taxa analyzed.

3) **Evaluate the weight of the scientific evidence of environmental hazard data.**
During risk evaluation, EPA plans to evaluate and integrate the environmental hazard evidence

identified in the literature inventory using the methods described in the *Application of Systematic Review in TSCA Risk Evaluation* (U.S. EPA, 2018).

4) **Consider the route(s) of exposure, based on reasonably available monitoring and modeling data, and other approaches to integrate exposure and hazard assessments.**
EPA plans to consider the aquatic (*e.g.*, water and sediment exposures) and terrestrial pathways in the HHCB conceptual model. These organisms may be exposed to HHCB via a number of environmental pathways (*e.g.*, surface water, sediment, air, soil, diet).

5) **Consider a persistent, bioaccumulative, and toxic (PBT) assessment of HHCB.**
EPA plans to consider the persistence, bioaccumulation, and toxic (PBT) potential of HHCB after reviewing relevant physical and chemical properties and exposure pathways. EPA plans to assess the reasonably available studies collected from the systematic review process relating to bioaccumulation and bioconcentration (*e.g.*, BAF, BCF) of HHCB. In addition, EPA plans to integrate traditional environmental hazard endpoint values (*e.g.*, LC_{50}, LOEC) and exposure concentrations (*e.g.*, surface water concentrations, tissue concentrations) for HHCB with the fate parameters (*e.g.*, BAF, BCF, BMF, TMF).

6) **Conduct an environmental risk estimation and characterization of HHCB.**
EPA plans to conduct a risk estimation and characterization of HHCB to identify whether there are risks to the aquatic and terrestrial environments from the measured and/or predicted concentrations of HHCB found in environmental media (*e.g.*, water, sediment, soil). Risk quotients (RQs) may be derived by the application of hazard and exposure benchmarks to characterize environmental risk (U.S. EPA, 1998; Barnthouse et al., 1982). Analysis of risk for characterization includes a confidence statement in risk estimation which qualitative judgment describing the certainty of the risk estimate considering the strength the evidence scores for hazard and exposure and the limitations, and relevance.

2.7.3.2 Human Health Hazards

EPA plans to analyze human health hazards as follows:

1) **Review reasonably available human health hazard data, including data from alternative test methods (*e.g.*, computational toxicology and bioinformatics; high-throughput screening methods; data on categories and read-across; *in vitro* studies; systems biology).**
EPA plans to evaluate human health studies using the evaluation strategies laid out in the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018) and updates to the epidemiological data quality criteria released with the first ten risk evaluations. The study evaluation results will be documented in the risk evaluation phase and data from acceptable studies will be extracted and integrated in the risk evaluation process.

   Mechanistic data may include analyses of alternative test data such as novel *in vitro* test methods and high throughput screening. The association between acute and chronic exposure scenarios to the agent and each health outcome will also be integrated. Study results will be extracted and presented in evidence tables or another appropriate format by organ/system.

2) **In evaluating reasonably available data, determine whether particular human receptor groups may have greater susceptibility to the chemical's hazard(s) than the general population.**
Reasonably available human health hazard data will be evaluated to ascertain whether some human receptor groups may have greater susceptibility than the general population to HHCB hazard(s). Susceptibility of particular human receptor groups to HHCB will be determined by evaluating information on factors that influence susceptibility.

EPA has reviewed some sources containing hazard information associated with potentially susceptible populations and lifestages such as pregnant women and infants. Pregnancy (*i.e.*, gestation) and childhood are potential susceptible lifestages for HHCB exposure. EPA may quantify these differences in the risk evaluation following further evaluation of the reasonably available data and information.

3) **Conduct hazard identification (the qualitative process of identifying non-cancer and cancer endpoints) and dose-response assessment (the quantitative relationship between hazard and exposure) for identified human health hazard endpoints.**
Human health hazards from acute and chronic exposures will be identified by evaluating the human and animal data that meet systematic review data quality criteria described in the methods described in the *Application of Systematic Review in TSCA Risk Evaluation* (U.S. EPA, 2018). Hazards identified by studies meeting data quality criteria will be grouped by routes of exposure relevant to humans (*e.g.*, oral, dermal, inhalation) and by cancer and noncancer endpoints identified in Section 2.4.2.

Dose-response assessment will be performed in accordance with EPA guidance (U.S. EPA, 2012a, 2011b, 1994) developing points of departure (POD) for either margins of exposure (MOEs), cancer slope factors (CSFs), oral slope factors (OSFs), and/or inhalation unit risks (IURs). Dose-response analyses may be used if the data meet data quality criteria and if additional information on the identified hazard endpoints are not reasonably available or would not alter the analysis.

The cancer mode of action (MOA) analyses determine the relevancy of animal data to human risk and how data can be quantitatively evaluated. If cancer hazard is determined to be applicable to HHCB, EPA plans to evaluate information on genotoxicity and the MOA for all cancer endpoints to determine the appropriate approach for quantitative cancer assessment in accordance with the *U.S. EPA Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a). In accordance with EPA's *Supplemental Guidance for Assessing Susceptibility from Early-life Exposures to Carcinogens* (U.S. EPA, 2005b), EPA plans to determine whether age-dependent adjustment factors (ADAFs) are appropriate for HHCB for specific conditions of use based upon potential exposures to children.

4) **Derive points of departure (PODs) where appropriate; conduct benchmark dose modeling depending on the reasonably available data. Adjust the PODs as appropriate to conform (*e.g.*, adjust for duration of exposure) to the specific exposure scenarios evaluated.**
Hazard data will be evaluated to determine the type of dose-response modeling that is applicable. Where modeling is feasible, a set of dose-response models that are consistent with a variety of potentially underlying biological processes will be applied to empirically model the dose-

response relationships in the range of the observed data consistent with EPA's *Benchmark Dose Technical Guidance Document* (U.S. EPA, 2012a). Where dose-response modeling is not feasible, NOAELs or LOAELs will be identified. Non-quantitative data will also be evaluated for contribution to weight of the scientific evidence or for evaluation of qualitative endpoints that are not appropriate for dose-response assessment.

EPA plans to evaluate whether the reasonably available PBPK and empirical kinetic models are adequate for route-to-route and interspecies extrapolation of the POD, or for extrapolation of the POD to standard exposure durations (*e.g.*, lifetime continuous exposure). If application of the PBPK model is not possible, oral PODs may be adjusted by $BW^{3/4}$ scaling in accordance with U.S. EPA (2011b), and inhalation PODs may be adjusted by exposure duration and chemical properties in accordance with U.S. EPA (1994).

5) **Evaluate the weight of the scientific evidence of human health hazard data.**
During risk evaluation, EPA plans to evaluate and integrate the human health hazard evidence identified in the literature inventory under acute and chronic exposure conditions using the methods described in the *Application of Systematic Review in TSCA Risk Evaluation* (U.S. EPA, 2018).

6) **Consider the route(s) of exposure (*e.g.*, oral, inhalation, dermal), reasonably available route-to-route extrapolation approaches; biomonitoring data; and approaches to correlate internal and external exposures to integrate exposure and hazard assessment.**
At this stage of review, EPA believes there will be sufficient reasonably available data to conduct a dose-response analysis and/or benchmark dose modeling for the oral route of exposure. EPA plans to also evaluate any potential human health hazards following dermal and inhalation exposure to HHCB, which could be important for worker, consumer and general population risk analysis. Reasonably available data will be assessed to determine whether or not a point of departure can be identified for the dermal and inhalation routes.

If sufficient reasonably available toxicity studies are not identified through the systematic review process to assess risks from inhalation or dermal exposure, then a route-to-route extrapolation may be needed. The preferred approach is to use a PBPK model (U.S. EPA, 2006a). Without an adequate PBPK model, considerations regarding the adequacy of data for route-to-route extrapolation are described in *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994). EPA may use these considerations when determining whether to extrapolate from the oral to the inhalation route of exposure. Similar approaches for oral-to-dermal route extrapolation are described in EPA guidance document *Risk Assessment Guidance for Superfund Volume I: Human Health Evaluation Manual (Part E, Supplemental Guidance for Dermal Risk Assessment)* (U.S. EPA, 2004).

If there are acceptable inhalation data after completion of systematic review, EPA may also consider extrapolating from the inhalation to the dermal route if first-pass metabolism through the liver via the oral route is expected because in that case, use of data from the oral route is not recommended (U.S. EPA, 1994). EPA may also consider inhalation-to-dermal route extrapolation if an inhalation toxicity study with a sensitive hazard endpoint is used to evaluate risks. Based on these considerations, EPA extrapolated from the inhalation to the dermal route

for several of the first ten risk evaluations under amended TSCA, including methylene chloride (U.S. EPA, 2020c) and carbon tetrachloride (U.S. EPA, 2020a).

7) **Conduct a human health risk estimation and characterization of HHCB.**
Analysis of risk for characterization includes a confidence statement in risk estimation. This confidence statement is based on qualitative judgment describing the certainty of the risk estimate considering the strength of the evidence scores for hazard and exposure along with their limitations and relevance. The lowest confidence evaluation for either hazard or exposure will drive the overall confidence estimate.

2.7.4 Summary of Risk Approaches for Characterization

Risk characterization is an integral component of the risk assessment process for both environmental and human health risks. EPA plans to derive the risk characterization in accordance with EPA's *Risk Characterization Handbook* (U.S. EPA, 2000). As defined in EPA's Risk Characterization Policy, "the risk characterization integrates information from the preceding components of the risk evaluation and synthesizes an overall conclusion about risk that is complete, informative and useful for decision makers" ((U.S. EPA, 2000)). Risk characterization is considered to be a conscious and deliberate process to bring all important considerations about risk, not only the likelihood of the risk but also the strengths and limitations of the assessment, and a description of how others have assessed the risk into an integrated picture.

The level of information contained in each risk characterization varies according to the type of assessment for which the characterization is written. Regardless of the level of complexity or information, the risk characterization for TSCA risk evaluations will be prepared in a manner that is transparent, clear, consistent, and reasonable (U.S. EPA, 2000) and consistent with the requirements of the *Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act* (82 FR 33726, July 20, 2017). As discussed in 40 CFR 702.43, risk characterization has a number of considerations. This is the step where EPA integrates the hazard and exposure assessments into risk estimates for the identified populations (including any PESS) and ecological characteristics and weighs the scientific evidence for the identified hazards and exposures. The risk characterization does not consider costs or other nonrisk factors, and takes into account, "where relevant, the likely duration, intensity, frequency, and number of exposures under the condition(s) of use…" The risk characterization also summarizes the following considerations: (1) uncertainty and variability in each step of the risk evaluation; (2) data quality, and any applicable assumptions used; (3) alternative interpretations of data and analyses, where appropriate; and (4) any considerations for environmental risk evaluations, if necessary (*e.g.*, related to nature and magnitude of effects).

EPA plans to also be guided by EPA's Information Quality Guidelines (U.S. EPA, 2002) as it provides guidance for presenting risk information. Consistent with those guidelines, EPA plans to identify in the risk characterization the following: (1) each population addressed by an estimate of applicable risk effects; (2) the expected risk or central estimate of risk for the PESS affected; (3) each appropriate upper-bound or lower-bound estimate of risk; (4) each significant uncertainty identified in the process of the assessment of risk effects and the studies that would assist in resolving the uncertainty; and (5) peer reviewed studies known to the Agency that support, are directly relevant to, or fail to support any estimate of risk effects and the methodology used to reconcile inconsistencies in the scientific information.

2.8 Peer Review

Peer review will be conducted in accordance with EPA's regulatory procedures for chemical risk evaluations, including using EPA's Peer Review Handbook (U.S. EPA, 2015b) and other methods consistent with Section 26 of TSCA (see 40 CFR 702.45). As explained in the Risk Evaluation Rule, the purpose of peer review is for the independent review of the science underlying the risk assessment. Peer review will therefore address aspects of the underlying science as outlined in the charge to the peer review panel such as hazard assessment, assessment of dose-response, exposure assessment, and risk characterization. The draft risk evaluation for HHCB will be peer-reviewed.

REFERENCES

Artola-Garciana, E. (2002). Distribution behaviour of polycyclic musks in sewage treatment plants and in biota. Interpretation of data using free and total concentration measurements. Utrecht, The Netherlands: Institute for Risk Assessment Sciences IRA.

Balk, F; Ford, RA. (1999). Environmental risk assessment for the polycyclic musks AHTN and HHCB in the EU. I. Fate and exposure assessment. Toxicol Lett 111: 57-79. https://www.ncbi.nlm.nih.gov/pubmed/10630703

Barnthouse, LW; DeAngelis, DL; Gardner, RH; O'Neill, RV; Suter, GW; Vaughan, DS. (1982). Methodology for environmental risk analysis. (ORNL/TM-8167). Oak Ridge, TN: Oak Ridge National Laboratory.

Butte, W; Ewald, F. (1999). Kinetics of accumulation and clearance of the polycyclic musk compounds Galaxolide (HHCB) and Tonalide (AHTN). Germany: University Oldenburg.

Cherrie, JW; Semple, S; Christopher, Y; Saleem, A; Hughson, GW; Philips, A. (2006). How important is inadvertent ingestion of hazardous substances at work? Ann Occup Hyg 50: 693-704. http://dx.doi.org/10.1093/annhyg/mel035

EU (European Union). (2008). European Union risk assessment report: 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-γ-2-benzopyran (HHCB). Luxembourg: European Union, European Chemicals Bureau, Institute for Health and Consumer Protection. https://echa.europa.eu/documents/10162/947def3b-bbbf-473b-bc19-3bda7a8da910

Howard, BE; Phillips, J; Miller, K; Tandon, A; Mav, D; Shah, MR; Holmgren, S; Pelch, KE; Walker, V; Rooney, AA; Macleod, M; Shah, RR; Thayer, K. (2016). SWIFT-Review: a text-mining workbench for systematic review. Syst Rev 5: 87. http://dx.doi.org/10.1186/s13643-016-0263-z

Hu, Z; Shi, Y; Cai, Y. (2011). Concentrations, distribution, and bioaccumulation of synthetic musks in the Haihe River of China. Chemosphere 84: 1630-1635.

Kinney, CA; Furlong, ET; Zaugg, SD; Burkhard, MR; Werner, SL; Cahill, JD; Jorgensen, GR. (2006). Survey of organic wastewater contaminants in biosolids destined for land application. Environ Sci Technol 40: 7207-7215. http://dx.doi.org/10.1021/es0603406

MacGillivray. (1966). Determination of vapor pressure for HHCB. Roy F. Weston study no. 95-040, report to research institute of fragrance materials. MacGillivray.

Muller, J; Bohmer, W; Bauer, A; Bernhardt, TH, Kurzawa, B.; Nowak, J. (2002). Untersuchung des stoffverhaltens von polyzklischen Moschus-verbindungen im klarschlamm und bodge (Band I und Band II). Schmallenbert, Germany: Fraunhofer-Insitut fur Molekulare Biologie and Angewandte Oekologie.

NLM (National Library of Medicine). (2018). Hazardous Substance Data Bank: Galaxolide, 1222-05-5. Available online

O'Neil MJ, E. (2013). The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals. In MJ O'Neil; PE Heckelman; PH Dobbelaar; KJ Roman; CM Kenney; LS Karaffa (Eds.), (15th ed.). Whitehouse Station, NJ: Merck Research Laboratories Division of Merck & Co., Inc.

OECD (Organisation for Economic Co-operation and Development). (2009a). 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-γ-2-benzopyran (HHCB) CAS No: 1222-05-5. SIDS dossier. UNEP Publications. https://hpvchemicals.oecd.org/ui/handler.axd?id=b36caa92-a554-4853-b98d-744e72cb9d56

OECD (Organisation for Economic Co-operation and Development). (2009b). Emission scenario document on plastic additives. (JT03267870). Paris, France: OECD Environmental Health and Safety Publications.

http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2004)8/rev1&doclanguage=en

OECD (Organisation for Economic Co-operation and Development). (2010). Emission scenario document on the blending of fragrance oils into commercial and consumer products. (JT03287706). Paris, France. https://www.oecd-ilibrary.org/docserver/9789264221031-en.pdf?expires=1588899868&id=id&accname=guest&checksum=CF6EE2468ED59303E11450A330FE0C5E

OECD (Organisation for Economic Co-operation and Development). (2019). Complementing document to the emission scenario document on plastic additives: Plastic additives during the use of end products. (JT03447969). Paris, France. http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/JM/MONO(2019)10&doclanguage=en

Sigma-Aldrich. (2019). Safety data sheet for 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran solution. https://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=US&language=en&productNumber=W520608&brand=ALDRICH&PageToGoToURL=https%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fproduct%2Faldrich%2Fw520608%3Flang%3Den

Simonich, SL; Begley, WM; Debaere, G; Echhoff, WS. (2000). Trace analysis of fragrance materials in water and treated wastewater. Environ Sci Technol 34: 959-965.

U.S. EPA (U.S. Environmental Protection Agency). (1994). Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry [EPA Report]. (EPA/600/8-90/066F). Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office. https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=71993&CFID=51174829&CFTOKEN=25006317

U.S. EPA (U.S. Environmental Protection Agency). (1998). Guidelines for ecological risk assessment [EPA Report]. (EPA/630/R-95/002F). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. https://www.epa.gov/risk/guidelines-ecological-risk-assessment

U.S. EPA (U.S. Environmental Protection Agency). (2000). Science policy council handbook: Risk characterization handbook [EPA Report]. (EPA/100/B-00/002). Washington, D.C.: U.S. Environmental Protection Agency, Science Policy Council. https://www.epa.gov/risk/risk-characterization-handbook

U.S. EPA (U.S. Environmental Protection Agency). (2002). Guidelines for ensuring and maximizing the quality, objectivity, utility, and integrity of information disseminated by the Environmental Protection Agency. (EPA/260/R-02/008). Washington, DC: U.S. Environmental Protection Agency, Office of Environmental Information. https://www.epa.gov/sites/production/files/2017-03/documents/epa-info-quality-guidelines.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2004). Risk Assessment Guidance for Superfund (RAGS), volume I: Human health evaluation manual, (part E: Supplemental guidance for dermal risk assessment). (EPA/540/R/99/005). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. http://www.epa.gov/oswer/riskassessment/ragse/index.htm

U.S. EPA (U.S. Environmental Protection Agency). (2005a). Guidelines for carcinogen risk assessment [EPA Report]. (EPA/630/P-03/001B). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. https://www.epa.gov/sites/production/files/2013-09/documents/cancer_guidelines_final_3-25-05.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2005b). Supplemental guidance for assessing susceptibility from early-life exposure to carcinogens [EPA Report]. (EPA/630/R-03/003F). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. https://www3.epa.gov/airtoxics/childrens_supplement_final.pdf

U.S. EPA. (U.S. Environmental Protection Agency). (2006a). Approaches for the application of physiologically based pharmacokinetic (PBPK) models and supporting data in risk assessment (Final Report) [EPA Report] (pp. 1-123). (EPA/600/R-05/043F). Washington, DC: U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=157668

U.S. EPA (U.S. Environmental Protection Agency). (2006b). A framework for assessing health risk of environmental exposures to children (pp. 1-145). (EPA/600/R-05/093F). Washington, DC: U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=158363

U.S. EPA (U.S. Environmental Protection Agency). (2011a). Exposure factors handbook: 2011 edition [EPA Report]. (EPA/600/R-090/052F). Washington, DC. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=236252

U.S. EPA (U.S. Environmental Protection Agency). (2011b). Recommended use of body weight 3/4 as the default method in derivation of the oral reference dose (pp. 1-50). (EPA/100/R-11/0001). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum, Office of the Science Advisor. https://www.epa.gov/sites/production/files/2013-09/documents/recommended-use-of-bw34.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2012a). Benchmark dose technical guidance. (EPA/100/R-12/001). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. https://www.epa.gov/risk/benchmark-dose-technical-guidance

U.S. EPA (U.S. Environmental Protection Agency). (2012b). Estimation Programs Interface Suite™ for Microsoft® Windows, v 4.11. Washington, DC. Retrieved from https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface

U.S. EPA (U.S. Environmental Protection Agency). (2014). TSCA work plan chemical risk assessment, HHCB, 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-γ-2-benzopyran, CASRN: 122-05-5. Washinton, DC: U.S. Environmental Protection Agency, Office of Chemical Safety and Pollution Prevention, Office of Pollution Prevention and Toxics. https://www.epa.gov/sites/production/files/2015-09/documents/hhcb_wp_ra_final_08_27_14.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2015a). ChemSTEER user guide - Chemical screening tool for exposures and environmental releases. Washington, DC. https://www.epa.gov/sites/production/files/2015-05/documents/user_guide.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2015b). Peer review handbook [EPA Report] (4th ed.). (EPA/100/B-15/001). Washington, DC: U.S. Environmental Protection Agency, Science Policy Council. https://www.epa.gov/osa/peer-review-handbook-4th-edition-2015

U.S. EPA (U.S. Environmental Protection Agency). (2017). Chemical data reporting (2012 and 2016 Public CDR database). Washington, DC: U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics. ChemView: June 2019. https://chemview.epa.gov/chemview

U.S. EPA (U.S. Environmental Protection Agency). (2018). Application of systematic review in TSCA risk evaluations. (740-P1-8001). Washington, DC: U.S. Environmental Protection Agency, Office of Chemical Safety and Pollution Prevention. https://www.epa.gov/sites/production/files/2018-06/documents/final_application_of_sr_in_tsca_05-31-18.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2019a). 40 CFR § 704.3: Definitions. (Code of Federal Regulations Title 40 Section 704.3). Washington, DC. https://www.govinfo.gov/app/details/CFR-2019-title40-vol33/CFR-2019-title40-vol33-sec704-3

U.S. EPA (U.S. Environmental Protection Agency). (2019b). Chemical Data Reporting (2012 and 2016 CBI CDR database) [Database]. U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics. http://www.epa.gov/cdr/

U.S. EPA (U.S. Environmental Protection Agency). (2019c). Chemistry Dashboard information for galaxolide. 1222-05-5. Available online at https://comptox.epa.gov/dashboard/dsstoxdb/results?search=DTXSID8027373

U.S. EPA. (U.S. Environmental Protection Agency). (2019d). CPCat: Chemical and Product Categories. https://actor.epa.gov/cpcat/faces/home.xhtml

U.S. EPA (U.S. Environmental Protection Agency). (2019e). Proposed designation of 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[γ]-2-benzopyran (HHCB; CASRN 1222-05-5) as a high-priority substance for risk evaluation. (EPA-HQ-OPPT-2018-0430-0010). Washington, DC. https://www.epa.gov/sites/production/files/2019-08/documents/134678-hexahydro-466788-hexamethylcyclopentag-2-benzopyran_1222-05-5_high-priority_proposeddesignation_082219_correct.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2019f). Use Report: 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8- hexamethylcyclopenta [g]-2-benzopyran (HHCB). Washington, DC: Office of Pollution Prevention and Toxics. https://www.epa.gov/sites/production/files/2019-08/documents/134678-hexahydro-466788-hexamethylcyclopentag-2-benzopyran_1222-05-5_high-priority_proposeddesignation_082219_correct.pdf

U.S. EPA. (U.S. Environmental Protection Agency). (2020a). Draft risk evaluation for carbon tetrachloride (methane, tetrachloro-); CASRN: 56-23-5 (pp. 1-301). (EPA-740-R1-8014). Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency. https://nepis.epa.gov/Exe/ZyPDF.cgi/P100YHUW.PDF?Dockey=P100YHUW.PDF

U.S. EPA. (U.S. Environmental Protection Agency). (2020b). Draft Scope of the Risk Evaluation for 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8- Hexamethylcyclopenta[?]-2-Benzopyran (HHCB) CASRN 1222-05-5. (EPA-740-D-20-013). https://www.epa.gov/sites/production/files/2020-04/documents/casrn-1222-05-5_134678-hexahydro-466788-hexamethylcyclopentag-2-benzopyran_hhcb_draft_scope.pdf

U.S. EPA. (U.S. Environmental Protection Agency). (2020c). Risk evaluation for methylene chloride (dichloromethane, dcm); CASRN: 75-09-2 (pp. 1-753). (EPA-740-R1-8010). Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency. https://www.epa.gov/sites/production/files/2020-06/documents/1_mecl_risk_evaluation_final.pdf

USGS (U.S. Geological Survey). (1991a). USGS Monitoring Data: National Water Quality Monitoring Council [Database]. Retrieved from http://www.waterqualitydata.us/portal/

USGS (U.S. Geological Survey). (1991b). USGS Monitoring Data: National Water Quality Monitoring Council - Groundwater. Retrieved from https://www.waterqualitydata.us/portal/#siteType=Aggregate%20groundwater%20use&sampleMedia=Water&mimeType=csv&dataProfile=activityAll

USGS (U.S. Geological Survey). (1991c). USGS Monitoring Data: National Water Quality Monitoring Council - Sediment. Retrieved from https://www.waterqualitydata.us/portal/#sampleMedia=Sediment&mimeType=csv

USGS (U.S. Geological Survey). (1991d). USGS Monitoring Data: National Water Quality Monitoring Council - Soil. Retrieved from https://www.waterqualitydata.us/portal/#sampleMedia=Soil&mimeType=csv

USGS (U.S. Geological Survey). (1991e). USGS Monitoring Data: National Water Quality Monitoring Council - Surface Water. Retrieved from https://www.waterqualitydata.us/portal/#siteType=Aggregate%20surface-water-use&sampleMedia=Water&mimeType=csv

Wiley-VCH. (2002). Ullmann's encyclopedia of industrial chemistry [Encyclopedia]. In B Elvers (Ed.), (6th ed.). Weinheim, Germany: Wiley-VCH. http://dx.doi.org/10.1002/14356007

Yang, JJ; Metcalfe, CD. (2006). Fate of synthetic musks in a domestic wastewater treatment plant and in an agricultural field amended with biosolids. Sci Total Environ 363: 149-165. http://dx.doi.org/10.1016/j.scitotenv.2005.06.022

Zviely, M. (2002). Aroma chemicals [Type of Work]. New York, NY: John Wiley & Sons.

APPENDICES

Appendix A ABBREVIATED METHODS FOR SEARCHING AND SCREENING

A.1 Literature Search of Publicly Available Databases

A.1.1 Search Term Genesis and Chemical Verification

To develop the chemical terms for the subsequent literature search for HHCB, several online sources were queried.

- California Department of Pesticide Regulation: https://www.cdpr.ca.gov/docs/chemical/monster2.htm
- U.S. EPA Chemistry Dashboard: https://comptox.epa.gov/dashboard
- University of Hertfordshire PPDB: Pesticide Properties DataBase: https://sitem.herts.ac.uk/aeru/ppdb/en/search.htm
- USEPA Reregistration Eligibility Decision (RED) documents: https://archive.epa.gov/pesticides/reregistration/web/html/status.html
- Office of Pesticide Programs Pesticide Chemical Search: https://ofmpub.epa.gov/apex/pesticides/f?p=CHEMICALSEARCH:1
- Food and Agriculture Organization of the United Nations: http://www.fao.org/home/en/
- PAN Pesticides Database: http://www.pesticideinfo.org/Search_Chemicals.jsp

Prior to inclusion in the search term string, all forms of chemical names were subjected to verification from several potential sources (*e.g.*, US EPA Chemistry Dashboard, STN International-CAS; see complete list of sources for chemical verification in Table_Apx A-1.). From these sources, all chemical names, synonyms, CAS number(s), trade names, *etc.* were documented and used to generate terms for database searches.

Table_Apx A-1. Sources of Verification for Chemical Names and Structures

Chemical Source	Contents	Document Location
Chemistry Dashboard (https://comptox.epa.gov/dashboard)	CAS Numbers, Synonyms, Structures, Properties, Environmental Fate and Transport.	Online
Dictionary of Chemical Names and Synonyms	Wide assortment of chemical compounds by chemical name and synonym, has CAS index and some structure data	ECOTOX
Farm Chemicals Handbook-1992	Pesticide information, CAS numbers and synonyms, some structure data ***Sometimes CAS number presented for a compound is for the main constituent only	ECOTOX

Chemical Source	Contents	Document Location
OPPT SMILES Verification Source	Structure Data	Electronic verification
RTECS (Registry of Toxic Effects of chemical substance, 1983-84 ed., 2 vols)	Chemical names, synonyms and CAS numbers	ECOTOX
Sigma – Aldrich website58784 http://www.sigma-aldrich.com	Organic and inorganic Compounds by chemical name, has CAS index and some structure and physical property data	Online
STN International (CAS) 1994	***Most complete source of chemical name, synonym and structure information, no physical properties	Online
The Pesticide Manual 10th edition, 1994	Pesticide Compounds by chemical name, synonym, product code, has CAS index and some structure and physical property data	ECOTOX
TSCA (Toxic Substances Control Act Chemical Substance Inventory, 1985 ed., 5 vols)	Chemical names, synonyms and CAS numbers	ECOTOX
World Wide Web (misc. web sources) A copy of the verification page is saved to the Attachments tab of the chemical entry. This includes company MSDS sheets or Chemical Labels.	Chemical names, synonyms and CAS numbers	Online
California Department of Pesticide Regulation (http://www.cdpr.ca.gov/dprdatabase.htm)	Multiple databases containing chemicals, pesticides, companies, products, *etc.*	Online
PAN Pesticide Database (http://www.pesticideinfo.org/Search_Chemicals.jsp)	Pesticides searchable by name or CAS #. Includes CAS #, Name, synonyms, targets, toxicity data, related chemicals and regulatory information.	Online
US EPA Office of Pesticide Programs Pesticide Fate Database – No web access available. An electronic copy of the data file is located at the Contractor site: PFATE_37_Tables.mdb.	Multiple databases containing chemicals, pesticides, companies, products, *etc.*	Online

A.1.2 Publicly Available Database Searches

The databases listed below were searched for literature containing the chemical search terms. Database searching occurred during April and May of 2019 by an information specialist and the results were stored in the Health and Environmental Research Online (HERO) database and assigned a HERO reference identification number.[5] The present literature search focused only on the chemical name (including synonyms and trade names) with no additional limits. Full details of the search strategy for each database are presented in Appendix A.1.2.1.

After initial deduplication in HERO[6], these studies were imported into SWIFT Review software (Howard et al., 2016) to identify those references most likely to be applicable to each discipline area (*i.e.* consumer, environmental, and general population exposure, occupational exposure and environmental releases, environmental hazards, human health hazards, fate, and physical and chemical properties).

A.1.2.1 Query Strings for the Publicly-Available Database Searches on HHCB

Table_Apx A-2 presents a list of the data sources, the search dates and number of peer-reviewed references resulting from the searches for HHCB. The sources are found as online databases and the resulting references were gathered and uploaded into the EPA Health and Environmental Research Online (HERO) database for literature screening.

Table_Apx A-2. Summary of Data Sources, Search Dates and Number of Peer-Reviewed Literature Search Results for HHCB

Source	Date of Search	Number of References
Current Contents	06/19/2019	518
Web of Science	09/13/2019	567
ProQuest CSA	06/19/2019	832
Dissertation Abstracts	06/20/2019	1
Science Direct	06/20/2019	102
Agricola	06/20/2019	145
TOXNET	06/20/2019	250
PubMed	07/03/2019	309
UNIFY	06/20/2019	56
Totals:		**2780**

[5] EPA's HERO database provides access to the scientific literature behind EPA science assessments. The database includes more than 600,000 scientific references and data from the peer-reviewed literature used by EPA to develop its regulations.
[6] Deduplication in HERO involves first determining whether a matching unique ID exists (*e.g.*, PMID, WOSid, or DOI). If one matches one that already exists in HERO, HERO will tag the existing reference instead of adding the reference again. Second, HERO checks if the same journal, volume, issue and page number are already in HERO. Third, HERO matches on the title, year, and first author. Title comparisons ignore punctuation and case.

GENERAL:
General search terms were compiled and used in the search strategies for each of the databases/sources listed below. Based upon the online search manuals for the respective databases/sources, it was necessary to construct searches as noted for each of the sources. The search terms are listed below in full for each source and noted if the general search terms or other search terms were used.

"(4R,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4R,7R)-rel-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4R,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4R,7S)-Galaxolide" OR "(4R,7S)-rel-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-cyclopenta[g]-2-benzopyran" OR "(4S,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-cyclopenta[g]-2-benzopyran" OR "(4S,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4S,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "4,6,6,7,8,8-Hexamethyl" OR "6-Ethyl-1,3,4,6,7,8-hexahydro-4,6,8,8-tetramethylcyclopenta[g]-2-benzopyran" OR "6-Ethyl-4,6,8,8-tetramethyl-1,3,4,6,7,8-hexahydroindeno[5,6-c]pyran" OR "8-Ethyl-1,3,4,6,7,8-hexahydro-4,6,6,8-tetramethylcyclopenta[g]-2-benzopyran" OR "8-Ethyl-4,6,6,8-tetramethyl-1,3,4,6,7,8-hexahydroindeno[5,6-c]pyran" OR "Abbalide" OR "Cyclopenta[f][2]benzopyran, 1,2,4,7,8,9-hexahydro-1,7,7,8,9,9-hexamethyl-" OR "Cyclopenta[g]-" OR "Cyclopenta[h]-2-benzopyran, 1,3,4,7,8,9-hexahydro-4,7,7,8,9,9-hexamethyl-" OR "EINECS 214-946-9" OR "Galaxolide" OR "Galaxolide 50" OR "Galaxolide 50BB" OR "Galaxolide 50IPM" OR "Galaxolide White" OR "Galoxolide" OR "Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-gamma-2-benzopyran" OR "Hexahydrohexamethyl cyclopentabenzopyran" OR "Hexahydrohexamethylcyclopentabenzopyran" OR "Indeno[5,6-c]pyran, 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethyl-" OR "Pearlide" OR "rel-(4R,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "rel-(4R,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "UNII-14170060AT"

CURRENT CONTENTS CONNECT:
Current Contents Connect may be accessed through EPA Desktop Library (https://intranet.epa.gov/desktop/databases.htm).

Date Searched: 06/19/19
Date Range of Search: 1998 to Present
N = 518

TS=("(4R,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4R,7R)-rel-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4R,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4R,7S)-Galaxolide" OR "(4R,7S)-rel-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-cyclopenta[g]-2-benzopyran" OR "(4S,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-cyclopenta[g]-2-benzopyran" OR "(4S,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4S,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "1,2,4,7,8,9-Hexahydro" OR "1,3,4,6,7,8-hexahidro" OR "1,3,4,6,7,8-Hexahydro" OR "1,3,4,6,7,8-HEXAHYDRO" OR "1,3,4,7,8,9-Hexahydro" OR "2,3,4,6,7,8-Hexahydro" OR "4,6,6,7,8,8-Hexamethyl" OR "6-Ethyl-1,3,4,6,7,8-hexahydro-4,6,8,8-tetramethylcyclopenta[g]-2-benzopyran" OR "6-Ethyl-4,6,8,8-tetramethyl-1,3,4,6,7,8-hexahydroindeno[5,6-c]pyran" OR "8-Ethyl-1,3,4,6,7,8-hexahydro-4,6,6,8-tetramethylcyclopenta[g]-2-benzopyran" OR "8-Ethyl-4,6,6,8-tetramethyl-1,3,4,6,7,8-hexahydroindeno[5,6-c]pyran" OR "Abbalide" OR "Cyclopenta[f][2]benzopyran, 1,2,4,7,8,9-hexahydro-1,7,7,8,9,9-hexamethyl-" OR "Cyclopenta[g]-"

OR "Cyclopenta[h]-2-benzopyran, 1,3,4,7,8,9-hexahydro-4,7,7,8,9,9-hexamethyl-" OR "EINECS 214-946-9" OR "Galaxolide" OR "Galaxolide 50" OR "Galaxolide 50BB" OR "Galaxolide 50IPM" OR "Galaxolide White" OR "Galoxolide" OR "Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-gamma-2-benzopyran" OR "Hexahydrohexamethyl cyclopentabenzopyran" OR "Hexahydrohexamethylcyclopentabenzopyran" OR "Indeno[5,6-c]pyran, 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethyl-" OR "Pearlide" OR "rel-(4R,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "rel-(4R,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "UNII-14170060AT")
N = 518

WOS Core Collection:
Web of Science Core Collection may be accessed through EPA Desktop Library (https://intranet.epa.gov/desktop/databases.htm) by clicking on the Web of Science Link or copying and pasting (https://apps.webofknowledge.com).

Date Searched: 09/13/2019
Date Range of Search: 1970 to Present
N = 567

TS=("(4R,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4R,7R)-rel-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4R,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4R,7S)-Galaxolide" OR "(4R,7S)-rel-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-cyclopenta[g]-2-benzopyran" OR "(4S,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-cyclopenta[g]-2-benzopyran" OR "(4S,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4S,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "1,2,4,7,8,9-Hexahydro" OR "1,3,4,6,7,8-hexahidro" OR "1,3,4,6,7,8-Hexahydro" OR "1,3,4,6,7,8-HEXAHYDRO" OR "1,3,4,7,8,9-Hexahydro" OR "2,3,4,6,7,8-Hexahydro" OR "4,6,6,7,8,8-Hexamethyl" OR "6-Ethyl-1,3,4,6,7,8-hexahydro-4,6,8,8-tetramethylcyclopenta[g]-2-benzopyran" OR "6-Ethyl-4,6,8,8-tetramethyl-1,3,4,6,7,8-hexahydroindeno[5,6-c]pyran" OR "8-Ethyl-1,3,4,6,7,8-hexahydro-4,6,6,8-tetramethylcyclopenta[g]-2-benzopyran" OR "8-Ethyl-4,6,6,8-tetramethyl-1,3,4,6,7,8-hexahydroindeno[5,6-c]pyran" OR "Abbalide" OR "Cyclopenta[f][2]benzopyran, 1,2,4,7,8,9-hexahydro-1,7,7,8,9,9-hexamethyl-" OR "Cyclopenta[g]-" OR "Cyclopenta[h]-2-benzopyran, 1,3,4,7,8,9-hexahydro-4,7,7,8,9,9-hexamethyl-" OR "EINECS 214-946-9" OR "Galaxolide" OR "Galaxolide 50" OR "Galaxolide 50BB" OR "Galaxolide 50IPM" OR "Galaxolide White" OR "Galoxolide" OR "Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-gamma-2-benzopyran" OR "Hexahydrohexamethyl cyclopentabenzopyran" OR "Hexahydrohexamethylcyclopentabenzopyran" OR "Indeno[5,6-c]pyran, 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethyl-" OR "Pearlide" OR "rel-(4R,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "rel-(4R,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "UNII-14170060AT")
N = 567

PROQUEST Agricultural and Environmental Science Database:
ProQuest Agricultural and Environmental Science Database may be accessed through EPA Desktop Library (https://intranet.epa.gov/desktop/databases.htm).

Date Searched: 06/19/19

Date Range of Search: 1900 to Present
N = 832

ALL("(4R,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4R,7R)-rel-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4R,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4R,7S)-Galaxolide" OR "(4R,7S)-rel-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-cyclopenta[g]-2-benzopyran" OR "(4S,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-cyclopenta[g]-2-benzopyran" OR "(4S,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4S,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "1,2,4,7,8,9-Hexahydro" OR "1,3,4,6,7,8-hexahidro" OR "1,3,4,6,7,8-Hexahydro" OR "1,3,4,6,7,8-HEXAHYDRO" OR "1,3,4,7,8,9-Hexahydro" OR "2,3,4,6,7,8-Hexahydro" OR "4,6,6,7,8,8-Hexamethyl" OR "6-Ethyl-1,3,4,6,7,8-hexahydro-4,6,8,8-tetramethylcyclopenta[g]-2-benzopyran" OR "6-Ethyl-4,6,8,8-tetramethyl-1,3,4,6,7,8-hexahydroindeno[5,6-c]pyran" OR "8-Ethyl-1,3,4,6,7,8-hexahydro-4,6,6,8-tetramethylcyclopenta[g]-2-benzopyran" OR "8-Ethyl-4,6,6,8-tetramethyl-1,3,4,6,7,8-hexahydroindeno[5,6-c]pyran" OR "Abbalide" OR "Cyclopenta[f][2]benzopyran, 1,2,4,7,8,9-hexahydro-1,7,7,8,9,9-hexamethyl-" OR "Cyclopenta[g]-" OR "Cyclopenta[h]-2-benzopyran, 1,3,4,7,8,9-hexahydro-4,7,7,8,9,9-hexamethyl-" OR "EINECS 214-946-9" OR "Galaxolide" OR "Galaxolide 50" OR "Galaxolide 50BB" OR "Galaxolide 50IPM" OR "Galaxolide White" OR "Galoxolide" OR "Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-gamma-2-benzopyran" OR "Hexahydrohexamethyl cyclopentabenzopyran" OR "Hexahydrohexamethylcyclopentabenzopyran" OR "Indeno[5,6-c]pyran, 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethyl-" OR "Pearlide" OR "rel-(4R,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "rel-(4R,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "UNII-14170060AT") AND STYPE("Scholarly Journals" OR Reports OR Thesis OR "Government Documents") AND LA(ENG)
N = 832

PROQUEST Dissertations and Theses:
ProQuest Dissertations and Theses may be accessed through the Kathryn A. Martin Library at the University of Minnesota at Duluth (https://libguides.d.umn.edu/az.php).

Date Searched: 06/20/19
Date Range of Search: 1900 to Present
N = 1

ALL("(4R,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4R,7R)-rel-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4R,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4R,7S)-Galaxolide" OR "(4R,7S)-rel-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-cyclopenta[g]-2-benzopyran" OR "(4S,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-cyclopenta[g]-2-benzopyran" OR "(4S,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4S,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "1,2,4,7,8,9-Hexahydro" OR "1,3,4,6,7,8-hexahidro" OR "1,3,4,6,7,8-Hexahydro" OR "1,3,4,6,7,8-HEXAHYDRO" OR "1,3,4,7,8,9-Hexahydro" OR "2,3,4,6,7,8-Hexahydro" OR "4,6,6,7,8,8-Hexamethyl" OR "6-Ethyl-1,3,4,6,7,8-hexahydro-4,6,8,8-tetramethylcyclopenta[g]-2-benzopyran" OR "6-Ethyl-4,6,8,8-tetramethyl-1,3,4,6,7,8-hexahydroindeno[5,6-c]pyran" OR "8-Ethyl-1,3,4,6,7,8-hexahydro-4,6,6,8-tetramethylcyclopenta[g]-2-benzopyran" OR "8-Ethyl-4,6,6,8-tetramethyl-1,3,4,6,7,8-hexahydroindeno[5,6-c]pyran" OR "Abbalide"

OR "Cyclopenta[f][2]benzopyran, 1,2,4,7,8,9-hexahydro-1,7,7,8,9,9-hexamethyl-" OR "Cyclopenta[g]-" OR "Cyclopenta[h]-2-benzopyran, 1,3,4,7,8,9-hexahydro-4,7,7,8,9,9-hexamethyl-" OR "EINECS 214-946-9" OR "Galaxolide" OR "Galaxolide 50" OR "Galaxolide 50BB" OR "Galaxolide 50IPM" OR "Galaxolide White" OR "Galoxolide" OR "Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-gamma-2-benzopyran" OR "Hexahydrohexamethyl cyclopentabenzopyran" OR "Hexahydrohexamethylcyclopentabenzopyran" OR "Indeno[5,6-c]pyran, 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethyl-" OR "Pearlide" OR "rel-(4R,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "rel-(4R,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "UNII-14170060AT") AND LA(ENG)
N = 1

SCIENCE DIRECT:
Science Direct may be accessed through the EPA Desktop Library (https://intranet.epa.gov/desktop/databases.htm).

Date Searched: 06/20/19
Date Range of Search: 1823 to Present
N = 102

Science Direct 01:
"(4R,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4R,7R)-rel-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4R,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4R,7S)-Galaxolide" OR "(4R,7S)-rel-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-cyclopenta[g]-2-benzopyran" OR "(4S,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-cyclopenta[g]-2-benzopyran" OR "(4S,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4S,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "1,2,4,7,8,9-Hexahydro"
N = 0

Science Direct 02:
"1,3,4,6,7,8-hexahidro" OR "1,3,4,6,7,8-Hexahydro" OR "1,3,4,6,7,8-HEXAHYDRO" OR "1,3,4,7,8,9-Hexahydro" OR "2,3,4,6,7,8-Hexahydro" OR "4,6,6,7,8,8-Hexamethyl" OR "6-Ethyl-1,3,4,6,7,8-hexahydro-4,6,8,8-tetramethylcyclopenta[g]-2-benzopyran" OR "6-Ethyl-4,6,8,8-tetramethyl-1,3,4,6,7,8-hexahydroindeno[5,6-c]pyran" OR "8-Ethyl-1,3,4,6,7,8-hexahydro-4,6,6,8-tetramethylcyclopenta[g]-2-benzopyran"
N = 69

Science Direct 03:
"8-Ethyl-4,6,6,8-tetramethyl-1,3,4,6,7,8-hexahydroindeno[5,6-c]pyran" OR "Abbalide" OR "Cyclopenta[f][2]benzopyran, 1,2,4,7,8,9-hexahydro-1,7,7,8,9,9-hexamethyl-" OR "Cyclopenta[g]-" OR "Cyclopenta[h]-2-benzopyran, 1,3,4,7,8,9-hexahydro-4,7,7,8,9,9-hexamethyl-" OR "EINECS 214-946-9" OR "Galaxolide" OR "Galaxolide 50" OR "Galaxolide 50BB"
N = 16

Science Direct 04:
"Galaxolide 50IPM" OR "Galaxolide White" OR "Galoxolide" OR "Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-gamma-2-benzopyran" OR "Hexahydrohexamethyl cyclopentabenzopyran" OR

"Hexahydrohexamethylcyclopentabenzopyran" OR "Indeno[5,6-c]pyran, 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethyl-" OR "Pearlide" OR "rel-(4R,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran"
N = 17

Science Direct 05:
"rel-(4R,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "UNII-14170060AT"
N = 0

AGRICOLA:
Agricola may be accessed through the EPA Desktop Library (https://intranet.epa.gov/desktop/databases.htm) or within the EndNote environment.

Date Searched: 06/20/19
Date Range of Search: 15th century to the Present
N = 145

Agricola 01:
(4R,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran
(4R,7R)-rel-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran
(4R,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran
(4R,7S)-Galaxolide
(4R,7S)-rel-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-cyclopenta[g]-2-benzopyran
(4S,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-cyclopenta[g]-2-benzopyran
(4S,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran
(4S,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran
1,2,4,7,8,9-Hexahydro
1,3,4,6,7,8-hexahidro
N = 0

Agricola 02:
1,3,4,6,7,8-Hexahydro
1,3,4,6,7,8-HEXAHYDRO
1,3,4,7,8,9-Hexahydro
2,3,4,6,7,8-Hexahydro
4,6,6,7,8,8-Hexamethyl
6-Ethyl-1,3,4,6,7,8-hexahydro-4,6,8,8-tetramethylcyclopenta[g]-2-benzopyran
6-Ethyl-4,6,8,8-tetramethyl-1,3,4,6,7,8-hexahydroindeno[5,6-c]pyran
8-Ethyl-1,3,4,6,7,8-hexahydro-4,6,6,8-tetramethylcyclopenta[g]-2-benzopyran
8-Ethyl-4,6,6,8-tetramethyl-1,3,4,6,7,8-hexahydroindeno[5,6-c]pyran
Abbalide
N = 0

Agricola 03:
Cyclopenta[f][2]benzopyran, 1,2,4,7,8,9-hexahydro-1,7,7,8,9,9-hexamethyl-
Cyclopenta[g]-

Cyclopenta[h]-2-benzopyran, 1,3,4,7,8,9-hexahydro-4,7,7,8,9,9-hexamethyl-
EINECS 214-946-9
Galaxolide
Galaxolide 50
Galaxolide 50BB
Galaxolide 50IPM
Galaxolide White
Galoxolide
N = 143

Agricola 04:
Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-gamma-2-benzopyran
Hexahydrohexamethyl cyclopentabenzopyran
Hexahydrohexamethylcyclopentabenzopyran
Indeno[5,6-c]pyran, 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethyl-
Pearlide
rel-(4R,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran
rel-(4R,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran
UNII-14170060AT
N = 2

TOXNET/(Toxline):
TOXNET(Toxline) may be accessed through the EPA Desktop Library (https://intranet.epa.gov/desktop/databases.htm).

Date Searched: 06/20/19
Date Range of Search: 1900 to Present
N = 250

TOXNET 01:
1222-05-5 OR 172339-62-7 OR 172339-63-8 OR 252332-95-9 OR 252332-96-0
N = 247

TOXNET 02:
252933-48-5 OR 252933-49-6 OR 1222-06-6 OR 857091-61-3 OR 102296-64-0
N = 1

TOXNET 03:
135546-43-9 OR 135546-42-8 OR 114109-63-6 OR 114109-62-5 OR 78448-48-3
N = 1

TOXNET 04:
78448-49-4 OR 80450-66-4
N = 1

PubMed:
PubMed may be accessed through the EPA Desktop Library (https://www.ncbi.nlm.nih.gov/pubmed/)

Date Searched: 07/03/2019
Date Range of Search: 1900 to present
N = 309

"4,6,6,7,8,8-Hexamethyl" OR "Abbalide" OR "Galaxolide" OR "Galoxolide" OR "Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-gamma-2-benzopyran" OR "Pearlide"
N = 309

Other search terms removed as PubMed noted Quoted Phrase not found. The quoted phrase was the chemical search terms.

ECOTOX UNIFY:
This is an internal EPA database that is not accessible to the public. Results from the ECOTOX Unify search strategy.

Date Searched: 06/20/19
Date Range of Search: all years
N = 56

HHCB

Terms Used -
(4R,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran
(4R,7R)-rel-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran
(4R,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran
(4R,7S)-Galaxolide
(4R,7S)-rel-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-cyclopenta[g]-2-benzopyran
(4S,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-cyclopenta[g]-2-benzopyran
(4S,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran
(4S,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran
1,2,4,7,8,9-Hexahydro
1,3,4,6,7,8-hexahidro
1,3,4,6,7,8-Hexahydro
1,3,4,6,7,8-HEXAHYDRO
1,3,4,7,8,9-Hexahydro
2,3,4,6,7,8-Hexahydro
4,6,6,7,8,8-Hexamethyl
6-Ethyl-1,3,4,6,7,8-hexahydro-4,6,8,8-tetramethylcyclopenta[g]-2-benzopyran
6-Ethyl-4,6,8,8-tetramethyl-1,3,4,6,7,8-hexahydroindeno[5,6-c]pyran
8-Ethyl-1,3,4,6,7,8-hexahydro-4,6,6,8-tetramethylcyclopenta[g]-2-benzopyran
8-Ethyl-4,6,6,8-tetramethyl-1,3,4,6,7,8-hexahydroindeno[5,6-c]pyran
Abbalide
Cyclopenta[f][2]benzopyran, 1,2,4,7,8,9-hexahydro-1,7,7,8,9,9-hexamethyl-
Cyclopenta[g]-

Cyclopenta[h]-2-benzopyran, 1,3,4,7,8,9-hexahydro-4,7,7,8,9,9-hexamethyl-
EINECS 214-946-9
Galaxolide
Galaxolide 50
Galaxolide 50BB
Galaxolide 50IPM
Galaxolide White
Galoxolide
Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-gamma-2-benzopyran
Hexahydrohexamethyl cyclopentabenzopyran
Hexahydrohexamethylcyclopentabenzopyran
Indeno[5,6-c]pyran, 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethyl-
Pearlide
rel-(4R,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran
rel-(4R,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran
UNII-14170060AT

A.1.2.2 Data Prioritization for Environmental Hazard, Human Health Hazard, Fate, and Physical and Chemical Properties

SWIFT Review has pre-set literature search strategies ("filters") developed by information specialists that can be applied to identify studies that are more likely to be useful for identifying human health and ecotoxicity content from those that likely do not (*e.g.*, analytical methods). The filters function like a typical search strategy where studies are tagged as belonging to a certain filter if the terms in the filter literature search strategy appear in title, abstract, keyword or medical subject headings (MeSH) fields content. The applied SWIFT Review filters focused on lines of evidence: human, animal models for human health, ecological taxa (which includes ecotoxicological animal models, plants, and other taxa), and *in vitro* studies. The details of the search strategies that underlie the filters are available online. Studies not retrieved using these filters were not considered further. Studies that included one or more of the search terms in the title, abstract, keyword, or MeSH fields were exported as a RIS file for screening in SWIFT-ActiveScreener or DistillerSR[7].

A.1.2.3 Data Prioritization for Occupational Exposures and Environmental Releases and General Population, Consumer and Environmental Exposures

To prioritize references related to occupational exposure, environmental release, general population exposure, consumer exposure, and environmental exposure, EPA used positive and negative seed studies to build a classification model in SWIFT Review. The positive seeds were identified using relevant literature pool for the first ten TSCA risk evaluations, while the negative seeds were identified from a subset of literature for the current high-priority substances. The model was then applied to the unclassified literature to generate a classification score for each reference. Scores above a certain threshold value were then prioritized for further review in SWIFT-ActiveScreener.

A.2 Peer-reviewed Screening Process

The studies identified from publicly available database searches and SWIFT-Review filtering/prioritization were housed in HERO system and imported into SWIFT-ActiveScreener or DistillerSR for title/abstract and full-text screening. Both title/abstract and full-text screening were

[7] DistillerSR is a web-based systematic review software used to screen studies available at https://www.evidencepartners.com/products/distillersr-systematic-review-software.

conducted by two independent reviewers. Screening is initiated with a pilot phase of screening (between 10 and 50) studies to identify areas where clarification in screening criteria might be needed or chemical-specific supplemental material tags might be identified. Records that met PECO or equivalent criteria (Appendix A.2.1) during title/abstract screening were considered for full-text screening. At both the title/abstract and full-text review levels, screening conflicts were resolved by discussion among the primary screeners. For citations with no abstract, the articles are initially screened based on all or some of the following: title relevance (titles that suggest a record is not relevant can be excluded rather than marked as unclear), and page numbers (articles two pages in length or less were assumed to be conference reports, editorials, or letters). During title/abstract or full-text level screening in DistillerSR, studies that did not meet the PECO criteria, but which could provide supporting information were categorized (or "tagged") as supplemental information.

It is important to emphasize that being tagged as supplemental material does not mean the study would necessarily be excluded from consideration in an assessment. The initial screening level distinctions between a study meeting the PECO criteria and a supplemental study are often made for practical reasons and the tagging structures (as seen in the literature inventory trees and heat maps in Section 2.1 of this document) are designed to ensure the supplemental studies are categorized for easy retrieval if needed while conducting the assessment. The impact on the assessment conclusions of individual studies tagged as supporting material is often difficult to assess during the screening phase of the assessment. These studies may emerge as being critically important to the assessment and need to be evaluated and summarized at the individual study level (*e.g.*, cancer MOA mechanistic or non-English-language studies), or be helpful to provide context (*e.g.*, summarize current levels of exposure, provide hazard evidence from routes or durations of exposure not pertinent to the PECO), or not be cited at all in the assessment (*e.g.*, individual studies that contribute to a well-established scientific conclusion). Studies maybe be tagged as supplemental material during either title/abstract or full-text screening. When tagged as supplemental material during title/abstract screening, it may not be completely clear whether the chemical of interest is reported in the study (*i.e.*, abstracts may not describe all chemicals investigated). In these cases, studies are still tagged with the expectation that if full-text retrieval is pursued, then additional screening would be needed to clarify if the study is pertinent.

A.2.1 Inclusion/Exclusion Criteria

A PECO statement is typically used to focus the research question(s), search terms, and inclusion/exclusion criteria in a systematic review. PECO criteria were developed *a priori* to screening and modified to fit the various discipline areas supporting the TSCA risk evaluations. Variations include the RESO (receptor, exposure, scenario/setting, and outcome) used for the engineering (occupational exposure and environmental releases) discipline, and PESO (pathways/processes, exposures, setting/scenario, and outcomes) used by the fate and transport discipline. All PECOs and PECO-equivalent criteria can be found in the following sections.

A.2.1.1 PECO for Environmental and Human Health Hazards

EPA developed a chemical-specific PECO statement (Table_Apx A-3) and potentially relevant supplemental material (Table_Apx A-4) to guide the screening of environmental and human health hazards data or information sources for HHCB.

Table_Apx A-3. Hazards Title and Abstract and Full-Text PECO Criteria for HHCB

PECO Element	Evidence
P	**Human:** Any population and life stage (*e.g.*, occupational or general population, including children and other sensitive populations). **Animal:** Aquatic and terrestrial species (live, whole organism) from any life stage (*e.g.*, preconception, in utero, lactation, peripubertal, and adult stages). Animal models will be inventoried according to the categorization below: Human health models: rat, mouse, rabbit, dog, hamster, guinea pig, cat, non-human primate, pig, hen (neurotoxicity only) Ecotoxicological models: invertebrates (*e.g.*, insects, spiders, crustaceans, mollusks, and worms) and vertebrates (*e.g.*, mammals and all amphibians, birds, fish, and reptiles). All hen studies (including neurotoxicity studies) will be included for ecotoxicological models. **Plants:** All aquatic and terrestrial species (live), including algal, moss, lichen and fungi species. **Screener note:** To identify human health and environmental hazards, other organisms not listed above in their respective categories can also be used. Non-mammalian model systems are increasingly used to identify potential human health hazards (*e.g.*, Xenopus, zebrafish), and traditional human health models (*e.g.*, rodents) can be used to identify potential environmental hazard. Neurotoxicity studies performed in hens (*e.g.*, OECD 418 and 419) are considered relevant to both human and eco hazard PECO considerations should be directed toward effects on target species only and not on the indirect effects expressed in taxa as a result of chemical treatment (*e.g.*, substance is lethal to a targeted pest species leading to positive effects on plant growth due to diminished presence of the targeted pest species). Tests of the single toxicants in *in vitro* and *ex vivo* systems or on gametes, embryos, or plant or fungal sections capable of forming whole, new organisms will be tagged as potentially supplemental (mechanistic studies). Bacteria and yeast studies specific for assessing genotoxicity or mutagenicity (*e.g.*, Ames assay) will also be tagged as potentially supplemental (mechanistic studies) but are otherwise excluded. Studies on viruses are excluded.
E	**Relevant forms and isomers:** 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta [g]-2-benzopyran (CASRN 1222-05-5) **Isomers**: Cyclopenta[g]-2-benzopyran,1,3,4,6,7,8-hexahydro4,6,6,7,8,8-hexamethyl-, (4S,7S)-(CASRN 172339-62- Cyclopenta[g]-2-benzopyran,1,3,4,6,7,8-hexahydro4,6,6,7,8,8-hexamethyl-, (4R,7S)-(CASRN 172339-63-8) Cyclopenta[g]-2-benzopyran,1,3,4,6,7,8-hexahydro4,6,6,7,8,8-hexamethyl-, (4S,7R)-(CASRN 252332-95-9) Cyclopenta[g]-2-benzopyran,1,3,4,6,7,8-hexahydro4,6,6,7,8,8-hexamethyl-, (4R,7R)-(CASRN 252332-96-0) Cyclopenta[g]-2-benzopyran,1,3,4,6,7,8-hexahydro4,6,6,7,8,8-hexamethyl-, (4R,7R)-rel (CASRN 252933-48-5) Cyclopenta[g]-2-benzopyran,1,3,4,6,7,8-hexahydro4,6,6,7,8,8-hexamethyl-, (4R,7S) rel (CASRN 252933-49-6)

PECO Element	Evidence
	Cyclopenta[g]-2-benzopyran, 1,3,4,6,7,8-hexahydro-4,4,6,6,8,8-hexamethyl (CASRN 1222-06-6) Cyclopenta[g]-2-benzopyran, 1,3,4,6,7,8-hexahydro-3,6,6,7,8,8-hexamethyl (CASRN 857091-61-3) Cyclopenta[g]-1-benzopyran, 2,3,4,6,7,8-hexahydro-4,4,6,6,8,8-hexamethyl (CASRN 102296-64-0) Cyclopenta[g]-1-benzopyran,2,3,4,6,7,8hexahydro4,6,6,7,8,8-hexamethyl (CASRN 135546-43-9) Cyclopenta[g]-2-benzopyran, 1,3,4,6,7,8-hexahydro-1,6,6,7,8,8-hexamethyl (CASRN 135546-42-8) Cyclopenta[h]-2-benzopyran, 1,3,4,7,8,9-hexahydro-4,7,7,8,9,9-hexamethyl (CASRN 114109-63-6) Cyclopenta[f][2]benzopyran, 1,2,4,7,8,9-hexahydro-1,7,7,8,9,9-hexamethyl (CASRN 114109-62-5) Cyclopenta[g]-2-benzopyran, 6-ethyl1,3,4,6,7,8-hexahydro-4,6,8,8-tetramethyl (CASRN 78448-48-3) Cyclopenta[g]-2-benzopyran, 8-ethyl1,3,4,6,7,8-hexahydro-4,6,6,8-tetramethyl (CASRN 78448-49-4) For **synonyms** see the EPA Chemistry Dashboard. **Human:** Any exposure to 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta [g]-2-benzopyran (HHCB CASRN 1222-05-5) singularly or in mixture, including exposure as measured by internal concentrations of these chemicals or metabolites of these chemicals in a biological matrix (*i.e.* urine, blood, semen, *etc.*). **Animal:** Any exposure to 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta [g]-2-benzopyran (HHCB CASRN 1222-05-5) including via water (including environmental aquatic exposures), soil or sediment, diet, gavage, injection, dermal, and inhalation. **Plants:** Any exposure to 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta [g]-2-benzopyran (HHCB CASRN 1222-05-5) including via water, soil, sediment. **Screener notes:** Field studies with media concentrations (*e.g.*, surface water, interstitial water, soil, sediment) and/or body/tissue concentrations of animals or plants are to be identified as ***Supplemental*** if any biological effects are reported. Animal and plant studies involving exposures to mixtures will be included only if they also include exposure to 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta [g]-2-benzopyran (HHCB CASRN 1222-05-5) alone. Otherwise, animal and plant mixture studies will be tagged as ***Supplemental.*** Human mixture studies are **included**. Controlled outdoor experimental studies (*e.g.*, controlled crop/greenhouse studies, mesocosm studies, artificial stream studies) are considered to be laboratory studies (not field studies) because there is a known and prescribed exposure dose(s) and an evaluation of hazardous effect(s). Whereas field studies (*e.g.*, biomonitoring) where there is no prescribed exposure dose(s) will be excluded if there is no evaluated hazardous effect, and tagged as supplemental field, if there is an evaluated hazardous effect.
C	**Human:** A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta [g]-2-benzopyran (HHCB 1222-05-5), or exposure to 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta [g]-2-benzopyran (HHCB 1222-05-5) for shorter periods of time.

PECO Element	Evidence
	Animal and Plants: A concurrent control group exposed to vehicle-only treatment and/or untreated control (control could be a baseline measurement). **<u>Screener note</u>:** • If no control group is explicitly stated or implied (*e.g.*, by mention of statistical results that could only be obtained if a control group was present), the study will be marked as ***Unclear*** during Title/Abstract Screening. • All case series and case studies describing findings in a sample size of less than 20 people in any setting (*e.g.*, occupation, general population) will be tracked as ***Supplemental.*** Case-control, case-crossover, case-referent, case-only, case-specular, case-cohort, case-parent, nested case-control study designs are all ***Included*.**
O	**Human**: All health outcomes (cancer and noncancer) at the organ level or higher. **Animal and Plants**: All apical biological effects (effects measured at the organ level or higher) including bioaccumulation from laboratory studies with concurrently measured media and/or tissue concentrations. Apical endpoints include but are not limited to reproduction, survival and growth. **<u>Screener note</u>:** • **Measurable biological effects relevant for humans, animals and plants may include but are not limited to:** mortality, behavioral, population, cellular, physiological, growth, reproduction, systemic, point of contact (irritation and sensitization) effects • Effects measured at the cellular level of biological organization and below are to be tagged as supplemental, mechanistic.

Table_Apx A-4. Major Categories of Potentially Relevant Supplemental Material for HHCB

Category	Evidence
Mechanistic studies	All studies that report results at the cellular level and lower in both mammalian and non-mammalian model systems, including *in vitro*, *in vivo*, *ex vivo*, and *in silico* studies. These studies include assays for genotoxicity or mutagenicity using bacteria or yeast.
ADME, PBPK, and toxicokinetic	Studies designed to capture information regarding absorption, distribution, metabolism, and excretion (ADME), toxicokinetic studies, or physiologically based pharmacokinetic (PBPK) models.
Case reports or case series	Case reports ($n \leq 3$ cases) and case series (non-occupational) will be tracked as potentially relevant supplemental information.
Susceptible populations (no health outcome)	Studies that identify potentially susceptible subgroups; for example, studies that focus on a specific demographic, life stage, or genotype. This tag applies primarily during full-text screening. **Screener note:** if biological susceptibility issues are clearly present or <u>*strongly*</u> implied in the title/abstract, this supplemental tag may be applied at the title abstract level. If uncertain at title/abstract, do not apply this tag to the reference during title/abstract screening.
Mixture studies	Experimental mixture studies that are not considered PECO-relevant because they do not contain an exposure or treatment group assessing only the chemical of interest. Human health animal model and eco animal model/plant will be tagged separately for mixture studies.
Non-English records	Non-English records will be tracked as potentially relevant supplemental information.
Records with no original data	Records that do not contain original data, such as other agency assessments, informative scientific literature reviews, editorials or commentaries.

Category	Evidence
Conference abstracts	Records that do not contain sufficient documentation to support study evaluation and data extraction.
Field Studies	Field studies with media concentrations (*e.g.*, surface water, interstitial water, soil, sediment) and/or body/tissue concentrations of animals or plants if biological effects reported.
Isomer	PECO-relevant studies with an exposure to one of the identified isomers, if any.

A.2.1.2 PECO for Consumer, Environmental, and General Population Exposures

EPA developed a chemical-specific PECO statement to guide the screening of consumer, environmental, and general population exposure data or information sources for HHCB (Table_Apx A-5.).

Table_Apx A-5. Consumer, Environmental, and General Population Exposure Evidence Title/Abstract and Full-Text PECO Criteria for HHCB

PECO Element	Evidence
Population	**Human:** General population; consumers; bystanders in the home; near-facility populations (includes industrial and commercial facilities manufacturing, processing, or using the chemical substance); children; susceptible populations (life stages, preexisting conditions, genetic factors), pregnant women; lactating women, women of child-bearing age. Many human population groups may be exposed. No chemical-specific exclusions are suggested at this time.
	Environmental: aquatic species, terrestrial species, terrestrial plants, aquatic plants (field studies only)
Exposure	**Expected Primary Exposure Sources, Pathways, Routes:** Pathways: indoor air/vapor/mist; indoor dust; particles; outdoor/ambient air; surface water; biosolids; sediment; breastmilk; food items containing HHCB including fish; consumer product uses in the home (including consumer product containing chemical); Routes of Exposure: Inhalation, Oral, Dermal
Comparator (Scenario)	**Human:** Consider media-specific background exposure scenarios and use/source specific exposure scenarios as well as which receptors are and are not reasonably exposed across the projected exposure scenarios.
	Environmental Consider media-specific background exposure scenarios and use/source specific exposure scenarios as well as which receptors are and are not reasonably exposed across the projected exposure scenarios.
Outcomes for Exposure Concentration or Dose	**Human:** Acute, subchronic, and/or indoor air and water concentration estimates (mg/m^3 or mg/L). Both external potential dose and internal dose based on biomonitoring and reverse dosimetry mg/kg/day will be considered. Characteristics of consumer products or articles (weight fraction, emission rates, etc) containing HHCB
	Environmental: A wide range of ecological receptors will be considered (range depending on available ecotoxicity data) using surface water concentrations, sediment concentrations.

Table_Apx A-6. Pathways Identified as Supplemental for HHCB[a]

Chemical	Drinking Water	Ambient Air	Air Disposal	Land Disposal	Underground Disposal	Ground Water
HHCB	--	--	--	--	--	--

[a] Supplemental pathways refer to pathways addressed by other EPA administered statutes.
Studies tagged under these pathways provide media information that is not prioritized in the screening process.

A.2.1.3 RESO for Occupational Exposure and Environmental Releases

EPA developed a generic RESO statement to guide the screening of engineering and occupational exposure data or information sources for the TSCA risk evaluations. Data or information sources that comply with the inclusion criteria specified in the RESO statement are eligible for inclusion, considered for evaluation, and possibly included in the environmental release and occupational exposure assessments. On the other hand, data or information sources that fail to meet the criteria in the RESO statement are excluded from further consideration.

Assessors seek information on various chemical-specific engineering and occupational exposure data needs as part of the process of developing the exposure assessment for each risk evaluation. EPA uses the RESO statement (Table_Apx A-7) along with the information in Table_Apx A-8 when screening the engineering and occupational exposure data and information.

Table_Apx A-7. Inclusion Criteria for Data Sources Reporting Engineering and Occupational Exposure Data

RESO Element	Evidence
Receptors	• Humans: Workers, including occupational non-users • Environment: All environmental receptors (relevant release estimates input to Exposure) Please refer to the conceptual models for more information about the environmental and human receptors included in the TSCA risk evaluation.
Exposure	• Worker exposure to and relevant environmental releases of the chemical substance from occupational scenarios: Dermal and inhalation exposure routes (as indicated in the conceptual model) Oral route (as indicated in the conceptual model) Please refer to the conceptual models for more information about the routes and media/pathways included in the TSCA risk evaluation.
Setting or **S**cenario	• Any occupational setting or scenario resulting in worker exposure and relevant environmental releases (includes all manufacturing, processing, use, disposal.
Outcomes	• Quantitative estimates* of worker exposures and of relevant environmental releases from occupational settings • General information and data related and relevant to the occupational estimates*

* Metrics (*e.g.*, mg/kg/day or mg/m^3 for worker exposures, kg/site/day for releases) are determined by toxicologists for worker exposures and by exposure assessors for releases; also, the Engineering, Release and Occupational Exposure Data Needs (Table_Apx A-8) provides a list of related and relevant general information.
TSCA=Toxic Substances Control Act

Table_Apx A-8. Engineering, Environmental Release and Occupational Data Necessary to Develop the Environmental Release and Occupational Exposure Assessments

Objective Determined during Scoping	Type of Data [a]
General Engineering Assessment (may apply to Occupational Exposures and / or Environmental Releases)	Description of the life cycle of the chemical(s) of interest, from manufacture to end-of-life (*e.g.*, each manufacturing, processing, or use step), and material flow between the industrial and commercial life cycle stages. The total annual U.S. volume (lb/yr or kg/yr) of the chemical(s) of interest manufactured, imported, processed, and used; and the share of total annual manufacturing and import volume that is processed or used in each life cycle step. Description of processes, equipment, and unit operations during each industrial/ commercial life cycle step. Material flows, use rates, and frequencies (lb/site-day or kg/site-day and days/yr; lb/site-batch and batches/yr) of the chemical(s) of interest during each industrial/ commercial life cycle step. Note: if available, include weight fractions of the chemicals (s) of interest and material flows of all associated primary chemicals (especially water). Number of sites that manufacture, process, or use the chemical(s) of interest for each industrial/ commercial life cycle step and site locations. Concentration of the chemical of interest
Occupational Exposures	Description of worker activities with exposure potential during the manufacture, processing, or use of the chemical(s) of interest in each industrial/commercial life cycle stage. Potential routes of exposure (*e.g.*, inhalation, dermal). Physical form of the chemical(s) of interest for each exposure route (*e.g.*, liquid, vapor, mist) and activity. Breathing zone (personal sample) measurements of occupational exposures to the chemical(s) of interest, measured as time-weighted averages (TWAs), short-term exposures, or peak exposures in each occupational life cycle stage (or in a workplace scenario similar to an occupational life cycle stage). Area or stationary measurements of airborne concentrations of the chemical(s) of interest in each occupational setting and life cycle stage (or in a workplace scenario similar to the life cycle stage of interest). For solids, bulk and dust particle size characterization data. Dermal exposure data. Exposure duration (hr/day). Exposure frequency (days/yr). Number of workers who potentially handle or have exposure to the chemical(s) of interest in each occupational life cycle stage. PPE types employed by the industries within scope. EC employed to reduce occupational exposures in each occupational life cycle stage (or in a workplace scenario similar to the life cycle stage of interest), and associated data or estimates of exposure reductions.
Environmental Releases (to relevant environmental media)	Description of sources of potential environmental releases, including cleaning of residues from process equipment and transport containers, involved during the manufacture, processing, or use of the chemical(s) of interest in each life cycle stage. Estimated mass (lb or kg) of the chemical(s) of interest released from industrial and commercial sites to each environmental medium (water) and treatment and disposal methods (POTW), including releases per site and aggregated over all sites (annual release rates, daily release rates)

Objective Determined during Scoping	Type of Data [a]
	Release or emission factors. Number of release days per year. Waste treatment methods and pollution control devices employed by the industries within scope and associated data on release/emission reductions.

[a] These are the tags included in the full-text screening form. The screener makes a selection from these specific tags, which describe more specific types of data or information.
In addition to the data types listed above, EPA may identify additional data needs for mathematical modeling. These data needs will be determined on a case-by-case basis.
Abbreviations:
hr=Hour; kg=Kilogram(s); lb=Pound(s); yr=Year; PV=Particle volume; POTW=Publicly owned treatment works; PSD=Particle size distribution; TWA=Time-weighted average

A.2.1.4 PESO for Fate and Transport

EPA developed a generic PESO statement to guide the screening of environmental fate data or information sources for the TSCA risk evaluations. Data or information sources that comply with the inclusion criteria in the PESO statement are eligible for inclusion, considered for evaluation, and possibly included in the environmental fate assessment. On the other hand, data or information sources that fail to meet the criteria in the PESO statement are excluded from further consideration.

Assessors seek information on various chemical-specific fate endpoints and associated fate processes, environmental media and exposure pathways as part of the process of developing the environmental fate assessment for each risk evaluation. EPA uses the PESO statement (Table_Apx A-9) along with the information in Table_Apx A-10 when screening the fate data or information sources to ensure complete coverage of the processes, pathways and data or information relevant to the environmental fate and transport of the chemical substance undergoing risk evaluation.

Table_Apx A-9. Inclusion Criteria for Data or Information Sources Reporting Environmental Fate and Transport Data

PESO Element	Evidence
Pathways and **P**rocesses	Environmental fate, transport, partitioning and degradation behavior across environmental media to inform exposure pathways of the chemical substance of interest Exposure pathways included in the conceptual models: air, surface water, groundwater, wastewater, soil, sediment and biosolids. Processes associated with the target exposure pathways Bioconcentration and bioaccumulation Destruction and removal by incineration Please refer to the conceptual models for more information about the exposure pathways included in each TSCA risk evaluation.

PESO Element	Evidence
Exposure	Environmental exposure of environmental receptors (*i.e.*, aquatic and terrestrial organisms) to the chemical substance of interest, mixtures including the chemical substance, and/or its degradation products and metabolites Environmental exposure of human receptors, including any potentially exposed or susceptible subpopulations, to the chemical substance of interest, mixtures including the chemical substance, and/or its degradation products and metabolites Please refer to the conceptual models for more information about the environmental
Setting or **S**cenario	Any setting or scenario resulting in releases of the chemical substance of interest into the natural or built environment (*e.g.*, buildings including homes or workplaces, or wastewater treatment facilities) that would expose environmental (*i.e.*, aquatic and terrestrial organisms) or human receptors (*i.e.*, general population, and potentially exposed or susceptible subpopulation)
Outcomes	Fate properties which allow assessments of exposure pathways: Abiotic and biotic degradation rates, mechanisms, pathways, and products Bioaccumulation magnitude and metabolism rates Partitioning within and between environmental media (see Pathways and Processes)

Table_Apx A-10. Fate Endpoints and Associated Processes, Media, and Exposure Pathways Considered in the Development of the Environmental Fate Assessment

Fate Data Endpoint	Associated Process(es)	Associated Media/Exposure Pathways			
		Surface Water, Wastewater, Sediment	Soil, Biosolids	Groundwater	Air
Required Environmental Fate Data					
Abiotic reduction rates or half-lives	Abiotic reduction, Abiotic dehalogenation	X	X	X	
Aerobic biodegradation rates or half-lives	Aerobic biodegradation	X	X		
Anaerobic biodegradation rates or half-lives	Anaerobic biodegradation	X	X	X	
Aqueous photolysis (direct and indirect) rates or half-lives	Aqueous photolysis (direct and indirect)	X			
Atmospheric photolysis (direct and indirect) rates or half-lives	Atmospheric photolysis (direct and indirect)				X
Bioconcentration factor (BCF), Bioaccumulation factor (BAF)	Bioconcentration, Bioaccumulation	X	X		X

Fate Data Endpoint	Associated Process(es)	Associated Media/Exposure Pathways			
		Surface Water, Wastewater, Sediment	Soil, Biosolids	Groundwater	Air
Biomagnification and related information	Trophic magnification	X	X		X
Desorption information	Sorption, Mobility	X	X	X	
Destruction and removal by incineration	Incineration				X
Hydrolysis rates or half-lives	Hydrolysis	X	X	X	
K_{OC} and other sorption information	Sorption, Mobility	X	X	X	
Wastewater treatment removal information	Wastewater treatment	X	X		X
Supplemental (or Optional) Environmental Fate Data					
Abiotic transformation products	Hydrolysis, Photolysis, Incineration	X	X		X
Aerobic biotransformation products	Aerobic biodegradation	X	X		
Anaerobic biotransformation products	Anaerobic biodegradation	X	X	X	
Atmospheric deposition information	Atmospheric deposition				X
Coagulation information	Coagulation, Mobility	X		X	
Incineration removal information	Incineration				X

A.2.1.5 Generation of Hazard Heat Maps

As stated in Appendix A.1.2.2, SWIFT Review has pre-set literature search strategies ("filters") developed by information specialists that can be applied to identify studies that are more likely to be useful for identifying human health and ecotoxicity content. The filters function like a typical search strategy where studies are tagged as belonging to a certain filter if the terms in the filter literature search strategy appear in title, abstract, keyword or MeSH fields content.

After the completion of full-text screening for hazard data, all references tagged as included (or "PECO-relevant) were uploaded to the SWIFT Review tool for further filtering. The SWIFT Review filters applied at this phase focused on types of health outcomes included: "ADME", "PBPK", "cancer", "cardiovascular", "developmental", "endocrine", "gastrointestinal", "hematological and immune", "hepatic", "mortality", "musculoskeletal", "neurological", "nutritional and metabolic", "ocular and sensory", "renal", "reproductive", "respiratory", and "skin and connective tissue". The details of these health outcome search strategies that underlie the filters are available online. Studies that included one or more of the search terms in the title, abstract, keyword, or MeSH fields were exported and used to populate the Hazard Heat Map (Figure 2-10). Studies that were not retrieved using these filters were tagged as "No Tag". The evidence type listed in the heat map (*e.g.*, human, animal-human health model, animal- environmental model, and plant) was manually assigned to each reference by screeners during the full-text screening.

The health outcome tags were originally designed for vertebrate systems, and as such, did not conform well to plant evidence. Therefore, any plant studies tagged for: “cancer”, “cardiovascular”, “gastrointestinal”, “hematological and immune”, “hepatic”, “musculoskeletal”, “neurological”, “ocular and sensory” and “renal and respiratory” were manually reviewed and re-tagged to more appropriate health outcomes.

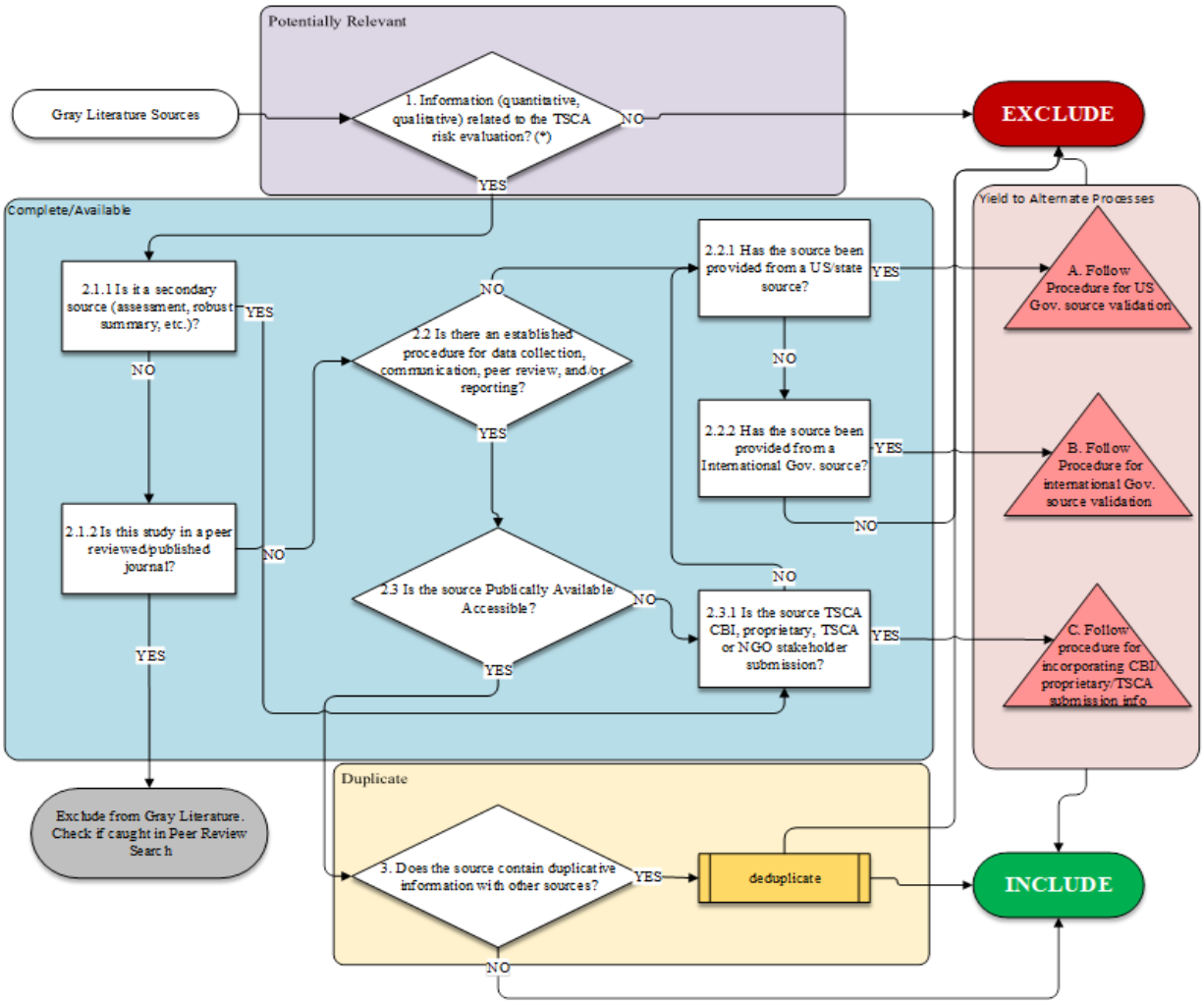
A.3 Gray Literature Search and Screening Strategies

EPA conducted a gray literature search for available information to support the TSCA risk evaluations for the next twenty TSCA risk evaluations. Gray literature is defined as the broad category of data/information sources not found in standard, peer-reviewed literature databases (*e.g.*, PubMed and Web of Science). Gray literature includes data/information sources such as white papers, conference proceedings, technical reports, reference books, dissertations, information on various stakeholder websites, and other databases. Given the nature of how gray literature is searched and collected, results may not come with a bibliographic citation or abstract and were therefore processed using a decision tree logic described in Appendix A.3.1 for potential relevance prior to entering full text screening where a discipline-specific PECO is applied.

Search terms were variable dependent on source and based on knowledge of a given source to provide discipline-specific information. A summary of sources and search terms are provided in Appendix A.3.4. The criteria for determining the potential relevance of documents identified from gray literature sources is described in the following sections for each discipline.

A.3.1 Screening of Gray Literature

To reduce the overall burden of processing gray literature results, EPA developed a screening process to determine the potential relevance of gray literature. This step was introduced prior to collecting the resulting documents. Figure_Apx A-1 describes the decision logic used to screen gray literature results.



Figure_Apx A-1. Decision Logic Tree Used to Screen Gray Literature Results

A.3.2 Initial Screening of Sources using Decision Logic Tree

The purpose of the inclusion/exclusion decision logic tree in Figure_Apx A-1 is to provide a broad, general screening technique to determine whether each gray literature source should be included and further screened or excluded with no additional screening necessary. The diamonds in the decision tree require analysis by the screener, whereas the rectangular boxes are used to classify the type of source. All the questions used in the decision process are provided in Table_Apx A-11.

Table_Apx A-11. Decision Logic Tree Overview

Step	Metric	Questions to Consider
1	Potential Relevance	Does the result have information (qualitative or quantitative) related to TSCA risk evaluations? *Apply Discipline relevancy metric
2.1.1	Complete / Available	Is it a secondary data source (assessment, robust summary, TSCA submission databases, *etc.*)?

Step	Metric	Questions to Consider
2.1.2		Is the document from a peer reviewed/published journal?
2.2		Is there an established procedure for data collection, communication, peer review, and/or reporting?
2.2.1		Has the data been provided by a US governmental/state source?
2.2.2		Has the data been provided by an international governmental source?
2.3		Are these data publicly available/accessible?
2.3.1		Is the source TSCA CBI, proprietary, TSCA or NGO stakeholder submission?
3	Duplicate	Does the result contain any duplicative information found in other sources?

Results of the gray literature search and decision tree process are included in Appendix A.3.4.

A.3.3 TSCA Submission Searching and Title Screening

EPA screens information submitted under TSCA Sections 4, 5, 8(e), and 8(d), as well as for your information (FYI) submissions. In the gray literature process defined in Appendix A.3.2, EPA considers the databases that contain TSCA submissions to be secondary sources (Step 1.1) because the metadata in the databases are secondary. These databases then advance to Step 2.3.1 and then to Process C. The Process C steps are described here.

EPA first screens the titles using two screeners per title. EPA conducts this step primarily to reduce the number of full studies to be obtained because some studies are available only on microfiche or in long-term storage. Screening is done using the inclusion and exclusion criteria within the relevant PECOs, PESOs or RESOs for each topic area (Appendix A.2.1). EPA excludes interim reports (*e.g.*, interim sacrifices for toxicity studies) and only final reports are further considered. If the title is not clear regarding the document's contents, EPA obtains the full text and advances to the next steps.

After full texts are obtained, EPA reviewed some sources (prior to full-text screening) based on whether they have several factors; primary data, an established procedure for peer review, data collection, communication and/or reporting and are publicly available. Sources that have these factors will move on to full text screening. Other sources will go straight to full text screening using PECO-type criteria without going through this extra step.

EPA may decide to initiate a backwards search on sources that are deemed to have secondary data. *In situ*ations where parameters such as procedures for peer review and data collection are unclear, EPA may reach out to the authors to retrieve information to gauge whether the source should be included or excluded. Studies that are not publicly available (such as proprietary or CBI sources) may undergo additional screening steps.

During the full-text screening step, two individuals screen each source according to the PECOs, PESOs and RESOs (Appendix A.2.1).

Results of the TSCA submission search and decision tree process are included in Appendix A.3.4.

A.3.4 Gray Literature Search Results for HHCB

Table_Apx A-12 provides a list of gray literature sources that yielded results for HHCB.

Table_Apx A-12. Gray Literature Sources that Yielded Results for HHCB

Source/Agency	Source Name	Source Type	Source Category	Source Website
Australian Government, Department of Health.	NICNAS Assessments (human health, Tier I, II or III)	International Resources	Assessment or Related Document	https://www.industrialchemicals.gov.au/chemical-information/search-assessments https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessments
ECHA	European Union Risk Assessment Report	International Resources	Assessment or Related Document	https://echa.europa.eu/information-on-chemicals/information-from-existing-substances-regulation
ECHA	ECHA Documents	International Resources	Assessment or Related Document	https://echa.europa.eu/information-on-chemicals
EPA	OPPT: TSCATS database maintained at SRC (TSCA submissions)	US EPA Resources	Database	
EPA	OPPT: Chemview (TSCA submissions - chemical test rule data and substantial risk reports)	US EPA Resources	Database	https://chemview.epa.gov/chemview
EPA	OPPT: CIS (CBI LAN) (TSCA submissions)	US EPA Resources	Database	
EPA	Office of Water: STORET and WQX	US EPA Resources	Database	https://www.waterqualitydata.us/portal/
EPA	TSCA Assessments	US EPA Resources	Assessment or Related Document	https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/assessments-conducted-tsca-work-plan-chemicals-prior

Source/Agency	Source Name	Source Type	Source Category	Source Website
EPA	TSCA Hazard Characterizations	US EPA Resources	Assessment or Related Document	https://ofmpub.epa.gov/oppthpv/hpv_hc_characterization.get_report_by_cas?doctype=2
EPA	EPA: AP-42	US EPA Resources	Regulatory Document or List	https://www.epa.gov/air-emissions-factors-and-quantification/ap-42-compilation-air-emissions-factors
EPA	Office of Air: CFRs and Dockets	US EPA Resources	Regulatory Document or List	https://www.epa.gov/stationary-sources-air-pollution
EPA	EPA: Generic Scenario	US EPA Resources	Assessment or Related Document	https://www.epa.gov/tsca-screening-tools/chemsteer-chemical-screening-tool-exposures-and-environmental-releases#genericscenarios
ILO	International Chemical Safety Cards (ICSCs)	International Resources	Database	https://www.ilo.org/safework/info/publications/WCMS_113134/lang--en/index.htm
KOECT	Kirk-Othmer Encyclopedia of Chemical Technology Journal Article	Other Resource	Encyclopedia	https://onlinelibrary.wiley.com/doi/book/10.1002/0471238961
OECD	OECD: General Site	International Resources	General Search	https://www.oecd.org/
OECD	OECD Emission Scenario Documents	International Resources	Assessment or Related Document	http://www.oecd.org/document/46/0,2340,en_2649_201185_2412462_1_1_1_1,00.html
RIVM	RIVM Reports: Risk Assessments	International Resources	Assessment or Related Document	https://www.rivm.nl/en

Appendix B PHYSICAL AND CHEMICAL PROPERTIES OF HHCB

Table_Apx B-1 summarizes statistics for the physical and chemical property values identified through systematic review as of June 2020. The "N" column indicates the number of unique primary sources of data for that endpoint. That is, if multiple sources presented equivalent values and cited the same primary source, only one of those was included in these statistics and included in the statistical calculations. All physical and chemical property values that were extracted and evaluated as of June 2020 are presented in the supplemental file *Data Extraction and Data Evaluation Tables for Physical and Chemical Property Studies* (EPA-HQ-OPPT-2018-0430).

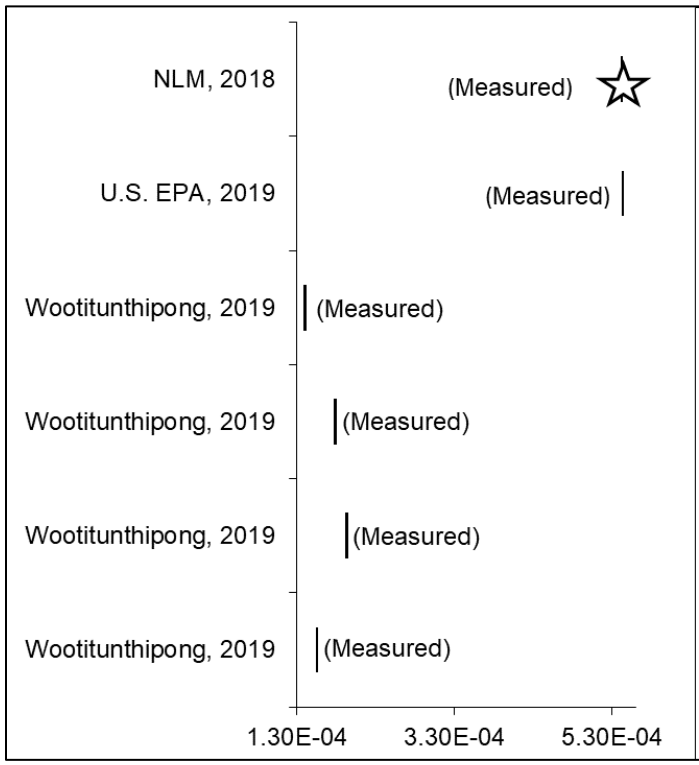
Table_Apx B-1. Summary Statistics for Reviewed Physical Properties

Property or Endpoint	*N*	Unit	Mean	Standard Deviation	Min	Max
Molecular formula	-	-	NA	NA	NA	NA
Molecular weight	-	g/mol	NA	NA	NA	NA
Physical state	3	-	NA	NA	NA	NA
Physical properties	2	-	NA	NA	NA	NA
Melting point	6	ºC	37	32	-5	58
Boiling point	5	ºC	290	90	129	342
Density	2	g/cm^3	1.0054	0	1.0054	1.0054
Vapor pressure	6	mm Hg	0.000296	0.000197	0.000143	0.000554
Vapor density	-	-	-	-	-	-
Water solubility	2	mg/L	1.75	0	1.75	1.75
Octanol/water partition coefficient (log Kow)	5	-	5.27	0.71	4.35	5.90
Henry's Law constant	0	$atm \cdot m^3/mol$	-	-	-	-
Flash point	0	ºC	-	-	-	-
Auto flammability	0	ºC	-	-	-	-
Viscosity	1	cP	12914	-	12914	12914
Refractive index	3	-	1.535	0.001	1.534	1.536
Dielectric constant	0	-	-	-	-	-

NA = Not applicable

The preliminarily selected value for vapor pressure lies outside the 95% confidence interval, defined as ±2 standard deviations from the mean under the assumption that the data are normally distributed (see Figure 2-12). Information about all reported vapor pressure values are summarized in Figure_Apx B-1 and presented in the supplemental file *Data Extraction and Data Evaluation Tables for Physical and*

Chemical Property Studies (EPA-HQ-OPPT-2018-0430). EPA plans to attempt to obtain and evaluate the primary data sources before identifying the vapor pressure value to be used in risk evaluation.



Reference	Value	Quality	Type
NLM, 2018	**5.45 x 10^{-4} mm Hg**	High	Measured
U.S.EPA, 2019	5.54 x 10^{-4} mm Hg	High	Measured
Wootitunthipong, 2019	1.95 x 10^{-4} mm Hg	High	Measured
Wootitunthipong, 2019	1.80 x 10^{-4} mm Hg	High	Measured
Wootitunthipong, 2019	1.43 x 10^{-4} mm Hg	High	Measured
Wootitunthipong, 2019	1.58 x 10^{-4} mm Hg	High	Measured

Bolded value represent proposed value for use in risk evaluation

Graph Legend

High Data Quality

Medium Data Quality

Low Data Quality

Proposed Value

Value reported as greater than (>)

Value reported as lesser than (<)

Figure_Apx B-1. Tornado Diagram for Vapor Pressure Data Identified in Systematic Review

Appendix C ENVIRONMENTAL FATE AND TRANSPORT PROPERTIES OF HHCB

Table_Apx C-1 provides the environmental fate characteristics that EPA identified and considered in developing the scope for HHCB. This information was presented in the *Proposed Designation of 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-Hexamethylcyclopenta[γ]-2-Benzopyran (HHCB; CASRN 1222-05-5) as a High-Priority Substance for Risk Evaluation* (U.S. EPA, 2019e) and may be updated as EPA collects additional information through systematic review methods.

Table_Apx C-1. Environmental Fate and Transport Properties of HHCB

Property or Endpoint	Value[a]	Reference
Direct Photodegradation	Direct photolysis is not expected to be an important fate process because HHCB does not contain chromophores that absorb at wavelengths >290 nm	NLM (2018)
	Direct photolysis by sunlight and gas-phase reaction with hydroxyl (·OH) radicals are considered to be the major degradation routes for HHCB in the atmosphere	OECD (2009a)
Indirect Photodegradation	Half-life ($t_{1/2}$) = 5 days (based on ·OH reaction rate constant of 2.6×10^{-11} cm^3/molecules·second at an OH concentration of 1.5×10^6 ·OH/cm^{-3})	OECD (2009a)
Hydrolysis	Stable; HHCB is not expected to undergo hydrolysis in the environment due to its chemical structure, which lacks functional groups known to undergo hydrolysis under environmental conditions	NLM (2018); OECD (2009a)
Biodegradation	0%/28 days CO_2 evolution test (OECD test guideline 301 B) (aerobic water)	NLM (2018); EU (2008)
	18%/200 days activated sludge; byproducts identified were galaxolide lactone and galaxolide hydroxy acid	NLM (2018) citing Balk and Ford (1999)
Removal in Wastewater Treatment	92% total removal (0.8% by biodegradation, 91% by sludge and 0.1% by volatilization to air; estimated)[b]	U.S. EPA (2012b)
	91.5% removal activated sludge plant	EU (2008) citing Simonich et al. (2000)
Bioconcentration Factor	1,584 (whole fish, wet weight) bluegill sunfish (*Lepomis macrochirus*) OECD Test guideline 305E	NLM (2018) citing Balk and Ford (1999)
	624 (fresh weight), 33,200 (lipid) zebrafish (*Brachydanio rerio*), OECD Test guideline 305E	EU (2008) citing Butte and Ewald (1999)
Bioaccumulation Factor	52,370 (crucian carp) 66,030 (common carp) 39,400 (silver carp)	Hu et al. (2011)

Property or Endpoint	Value[a]	Reference
Soil Organic Carbon:Water Partition Coefficient (Log K_{OC})	4.87	EU (2008) citing MacGillivray (1966)
	3.6–3.9	EU (2008) citing Muller et al. (2002)
	3.8	EU (2008) citing Artola-Garciana (2002)

[a] Measured unless otherwise noted

[b] EPI Suite™ physical property inputs: Log K_{OW} = 5.90, boiling point = 325 °C, melting point = -5 °C, vapor pressure = 0.000545 mm Hg, water solubility = 1.75 mg/L, biodegradation half-life (in hours) in the primary clarifier of a sewage treatment plant (STP; BioP) = 10,000, biodegradation half-life (in hours) in the aeration vessel of an STP (BioA) = 10,000 and biodegradation half-life (in hours) in the final settling tank of an STP (BioS) = 10,000, Simplified Molecular-Input Line-Entry System (SMILES): O(CC(c(c1cc(c2C(C3C)(C)C)C3(C)C)c2)C)C1

Appendix D REGULATORY HISTORY

HHCB is subject to federal and state laws and regulations in the United States (Table_Apx D-1 and Table_Apx D-2). Regulatory actions by other governments, tribes and international agreements applicable to HHCB are listed in Table_Apx D-3.

D.1 Federal Laws and Regulations

Table_Apx D-1. Federal Laws and Regulations

Statutes/ Regulations	Description of Authority/Regulation	Description of Regulation
EPA Statutes/Regulations		
TSCA Section 6(b)	EPA is directed to identify high-priority chemical substances for risk evaluation; and conduct risk evaluations on at least 20 high priority substances no later than three and one-half years after the date of enactment of the Frank R. Lautenberg Chemical Safety for the 21st Century Act.	HHCB is one of the 20 hemicals EPA designated as a High-Priority Substance for isk evaluation under TSCA 84 FR 71924, December 30, 019).
TSCA Section 8(a)	The TSCA Section 8(a) CDR Rule requires manufacturers (including importers) to give EPA basic exposure-related information on the types, quantities and uses of chemical substances produced domestically and imported into the United States.	HHCB manufacturing (including importing), processing and use information is reported under the CDR rule (85 FR 20122, April 2, 2020).
TSCA Section 8(b)	EPA must compile, keep current and publish a list (the TSCA Inventory) of each chemical substance manufactured (including imported) or processed in the United States.	HHCB was on the initial TSCA Inventory and therefore was not subject to EPA's new chemicals review process under TSCA Section 5 (60 FR 16309, March 29, 1995).
TSCA Section 8(e)	Manufacturers (including importers), processors, and distributors must immediately notify EPA if they obtain information that supports the conclusion that a chemical substance or mixture presents a substantial risk of injury to health or the environment.	One risk report was received for HHCB (May 1997) (U.S. EPA, ChemView, Accessed March 22, 2019).
Federal Insecticide, Fungicide, and Rodenticide Act	FIFRA governs the sale, distribution and use of pesticides. Section 3 of FIFRA generally requires that pesticide products be registered by EPA	HHCB is an approved nonfood use inert ingredient and as a

Statutes/ Regulations	Description of Authority/Regulation	Description of Regulation
(FIFRA) - Sections 3 and 6	prior to distribution or sale. Pesticides may only be registered if, among other things, they do not cause "unreasonable adverse effects on the environment." Section 6 of FIFRA provides EPA with the authority to cancel pesticide registrations if either (1) the pesticide, labeling, or other material does not comply with FIFRA; or (2) when used in accordance with widespread and commonly recognized practice, the pesticide generally causes unreasonable adverse effects on the environment.	component of a fragrance. (InertFinder, Accessed March 22, 2019).

D.2 State Laws and Regulations

Table_Apx D-2. State Laws and Regulations

State Actions	Description of Action
Chemicals of High Concern to Children	Minnesota includes HHCB in the list of chemicals of high concern (Toxic Free Kids Act Minn. Stat. 116.9401 to 116.9407).
Other	California lists HHCB as a designated priority chemical for biomonitoring (California SB 1379). The Oregon Department of Environmental Quality lists HHCB as a priority persistent pollutant (Oregon SB 737).

D.3 International Laws and Regulations

Table_Apx D-3. Regulatory Actions by other Governments, Tribes, and International Agreements

Country/ Organization	Requirements and Restrictions
European Union	HHCB is registered for use in the EU. (Chemicals Agency (ECHA) database, Accessed April 2, 2019).
Australia	HHCB was assessed under Human Health Tier II of the Inventory Multi-Tiered Assessment and Prioritisation (IMAP). Use reported include washing and cleaning products; air care products; anti-odour agents; floor and surface treatment products; scented clothes and papers; car care products; photochemicals; leather tanning and textile dyes; coatings and

Country/ Organization	Requirements and Restrictions
	paint thinners; polishes and wax blends; and adsorbents. (NICNAS, 2019, Accessed April 4, 2019).
Japan	HHCB is regulated in Japan under the following legislation: Act on the Evaluation of Chemical Substances and Regulation of Their Manufacture, *etc.* (Chemical Substances Control Law; CSCL) (NITE, 2019, Accessed April 4, 2019).

Appendix E PROCESS, RELEASE AND OCCUPATIONAL EXPOSURE INFORMATION

This appendix provides information and data found in preliminary data gathering for HHCB.

E.1 Process Information

Process-related information potentially relevant to the risk evaluation may include process diagrams, descriptions and equipment. Such information may inform potential release sources and worker exposure activities.

E.1.1 Manufacturing (Including Importing)

E.1.1.1 Manufacturing

HHCB is manufactured by a three-step reaction (Wiley-VCH, 2002; Zviely, 2002). First, a cycloaddition reaction of alpha.-methyl styrene and 2-methyl-2-butene (*i.e.*, amylene) is performed under acidic conditions to obtain 1,1,2,3,3-pentamethylindane (1). Second, the pentamethylindane (1) is hydroxyalkylated with propylene oxide in a Friedel-Crafts reaction using aluminum chloride as a catalyst. Third, the ring closure of the resulting 1,1,2,3,3- pentamethyl-5-(-hydroxyisopropyl)indane (2) to 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8- hexamethylcyclopenta-g-benzopyran (HHCB; Galaxolide) is accomplished with paraformaldehyde and a lower aliphatic alcohol via the acetal or with paraformaldehyde and a carboxylic acid anhydride via the acylate (U.S. EPA, 2014).

E.1.1.2 Importing

EPA has not identified specific activities related to the import of HHCB at this time. However, EPA anticipates that HHCB is shipped in bulk containers and may be repackaged into smaller containers for resale, such as drums or bottles. The type and size of container will vary depending on customer requirement. In some cases, QC samples may be taken at import and repackaging sites for analyses. Some import facilities may only serve as storage and distribution locations, and repackaging/sampling may not occur at all import facilities.

HHCB may be imported neat or as a component in a formulation. In the 2016 CDR, all eight companies reporting the import of HHCB also reported the maximum concentration of the formulation as over 90 percent HHCB (U.S. EPA, 2019b).

HHCB is imported into the U.S. for processing and distribution. Releases are not expected to result from import activities but may occur at import sites if HHCB is also diluted and compounded onsite after import, as further discussed below in the processing and distribution section.

E.1.2 Processing and Distribution

E.1.2.1 Incorporation into a Formulation, Mixture or Reaction Product

Incorporation into a formulation, mixture or reaction product refers to the process of mixing or blending of several raw materials to obtain a single product or preparation. HHCB is incorporated into formulations as an odor agent during the manufacture of chemical products, soaps, cleaning compounds, and fragrance mixtures (U.S. EPA, 2019b). HHCB-specific formulation processes were not identified; however, at least one Emission Scenario Document (ESD) published by the OECD has been identified that provide general process descriptions for these types of products.

E.1.2.2 Incorporation into an Article

Incorporation into an article typically refers to a process in which a chemical becomes an integral component of an article (as defined at 40 CFR 704.3) for distribution in commerce. Exact process operations involved in the incorporation of HHCB-containing formulations or reaction products are dependent on the article. HHCB and HHCB formulations or reaction products are incorporated into articles during the manufacturing of plastic material and resins. The ESD on Plastic Additives and the complementing document on Plastic Additives During the Use of End Products will be referenced to provide general process descriptions for the identified articles (OECD, 2019, 2009b).

E.1.2.3 Repackaging

EPA has not identified specific information for the repackaging of HHCB. EPA expects repackaging sites receive the chemical in bulk containers and transfer the chemical from the bulk container into another smaller container in preparation for distribution in commerce.

E.1.2.4 Recycling

EPA did not identify HHCB-specific information for recycling.

E.1.3 Uses

Musks are considered important compounds to the fragrance industry because of their unique odor properties, ability to improve the fixation of fragrance compounds, and ability to bind fragrances to fabrics. The function of HHCB in fragrance formulations is as both a fragrance and a fragrance enhancer.

HHCB is used as a fragrance ingredient in cleaning because it is alkali-stable and does not discolor in light. HHCB and other musks provide a unique, dominant scent in products. Because HHCB binds fragrances to fabric and skin, the scent is balanced and longer lasting. HHCB is often used in laundry detergent fragrances because it is one of the few chemicals that can leave a small residual fragrance on cloth after washing and can cover up odors from the detergent itself as well as from dirt in the wash solution. Synthetic musks, including HHCB, also may be used to mask chemical odors and can be found in products labeled "unscented," but do not seem to be added to products labeled "fragrance free" (U.S. EPA, 2014).

E.1.3.1 Air Care Products

2012 and 2016 CDR information indicated the use of HHCB in air care products (U.S. EPA, 2019b). Product SDS data and public comments identified HHCB in continuous action air fresheners such as candles, fragrance oils, scented bathroom clips, and air freshener plug-ins (U.S. EPA, 2019a)(EPA-HQ-OPPT-2018-0430-0012). HHCB is also found in motor vehicle air fresheners and instant action air fresheners such as aerosol sprays, pet deodorizer sprays, and car deodorizer sprays (U.S. EPA, 2019a).

Commercial uses of these items may include the use of air care products for professional cleaning, odor reduction near professional drivers, and deodorizing during car detailing.

E.1.3.2 Cleaning and Furnishing Care Products

2012 and 2016 CDR information indicated the use of HHCB in cleaning and furnishing care products (U.S. EPA, 2019b). Workers who use industrial or bulk cleaners everyday may have occupational exposure to HHCB. Staff in commercial kitchens or bathrooms, hotels, and any professional cleaning business may be included in the affected workers.

E.1.3.3 Laundry and Dishwashing Products

Laundry detergent and fabric softeners were identified as containing HHCB based on product SDS information and public comments (U.S. EPA, 2019a)(EPA-HQ-OPPT-2018-0430-0013).These products may present occupational exposure in commercial laundromats and businesses that provide linen services, such as hotels or resorts.

E.1.3.4 Plastic and Rubber Products Not Covered Elsewhere

EPA identified disposable floor mats and odor eliminating discs containing HHCB (U.S. EPA, 2019a) also received a CBI claim regarding other plastic and rubber products containing HHCB.

E.1.3.5 Paper Products

EPA did not identify specific paper products containing HHCB at this time.

E.1.3.6 Other Uses: Laboratory Chemical

A Safety Data Sheet for HHCB (<= 100% percent purity) indicates the recommended use as a laboratory chemical. However, specific laboratory use activities are unknown (Sigma-Aldrich, 2019). A commenter (EPA-HQ-OPPT-2019-0131-0051) provided descriptions of their use of HHCB in analytical standard, research, equipment calibration and sample preparation applications, including reference sample for analysis of terrestrial and extraterrestrial material samples, which the commenter also indicated was a critical use, further informing EPA's understanding of this condition of use.

E.1.4 Disposal

Each of the conditions of use of HHCB may generate waste streams of the chemical that are collected and transported to third-party sites for disposal, treatment, or recycling. Disposal of products and articles containing HHCB will also be considered (*e.g.*, paper products, plastics, *etc.*). Industrial sites that treat or dispose onsite wastes that they themselves generate will be assessed for each condition of use. Similarly, point source discharges of HHCB to surface water will be assessed for each condition of use.

Wastes of HHCB that are generated during a condition of use and sent to a third-party site for treatment, disposal, or recycling may include wastewater and solid waste. HHCB may be contained in wastewater discharged to POTW or other, non-public treatment works for treatment. Industrial wastewater containing HHCB discharged to a POTW may be subject to EPA or authorized NPDES state pretreatment programs. The assessment of wastewater discharges to POTWs and non-public treatment works of HHCB will be evaluated for each condition of use. Because of its properties, HHCB also partitions to solid phases in the wastewater treatment process (sludge), and with further treatment can become concentrated in biosolids. This organic carbon-rich material is disposed of by landfill or incineration or may be utilized for land application to enhance physical soil properties as well as plant yield.

Solid wastes are defined under Resource Conservation and Recovery Act (RCRA) as any material that is discarded by being: abandoned; inherently waste-like; a discarded military munition; or recycled in certain ways (certain instances of the generation and legitimate reclamation of secondary materials are exempted as solid wastes under RCRA).

E.2 Sources Containing Potentially Relevant Data or Information

There are currently no exposure limits for HHCB established by OSHA, NIOSH, or American Conference of Governmental Industrial Hygienists (ACGIH). Because of this, there have been no industrial health studies conducted by any of these organizations for possible worker exposure to HHCB.

Appendix F SUPPORTING INFORMATION – CONCEPTUAL MODEL FOR INDUSTRIAL AND COMMERCIAL ACTIVITIES AND USES

Table_Apx F-1. Worker and ONU Exposure Conceptual Model Supporting Table

Life Cycle Stage	Category	Subcategory	Release / Exposure Scenario	Exposure Pathway	Exposure Route	Receptor / Population	Plans to Evaluate	Rationale
Manufacturing	Domestic Manufacturing/ Importing	Domestic Manufacturing/ Importing	Manufacture of HHCB	Liquid Contact	Dermal	Workers	Yes	HHCB is manufactured as a liquid; therefore, EPA plans to evaluate dermal exposures for workers
				Solid Contact	Dermal	Workers	No	HHCB is manufactured as a liquid; therefore, exposures to solids for workers are not expected
				Vapor	Inhalation	Workers, ONU	Yes	Due to its volatility (VP = 0.000545 mmHg) at room temperature, EPA plans to evaluate inhalation exposure
				Mist	Inhalation/ Dermal	Workers, ONU	No	Mist generation is not expected during Manufacturing
				Dust	Inhalation/ Dermal	Workers, ONU	No	HHCB is manufactured as a liquid; therefore, exposures to dust for workers are not expected
				Liquid/Solid Contact	Dermal	ONU	No	Dermal exposure by ONU is not expected for this condition of use as they are not expected to directly handle the chemical
	Importing	Importing	Repackaging of Import Containers	Liquid Contact	Dermal	Workers	Yes	The potential for dermal exposure to workers exists during import, but exposure will only occur in the event the imported material is repackaged
				Solid Contact	Dermal	Workers	Yes	HHCB could be imported as a solid; therefore, dermal exposures for workers are expected
				Vapor	Inhalation	Workers, ONU	Yes	Due to its volatility (VP = 0.000545 mmHg) at room temperature, EPA plans to evaluate inhalation pathway
				Mist	Inhalation/ Dermal	Workers, ONU	No	Mist generation is not expected during import or repackaging
				Dust	Inhalation/ Dermal	Workers, ONU	Yes	HHCB could be imported as a solid; therefore, exposures to dust for workers are expected
				Liquid/Solid Contact	Dermal	ONU	No	Dermal exposure by ONU is not expected for this condition of use as they are not expected to directly handle the chemical

Life Cycle Stage	Category	Subcategory	Release / Exposure Scenario	Exposure Pathway	Exposure Route	Receptor / Population	Plans to Evaluate	Rationale
Processing	Repackaging	Odor agent (in all other chemical product and preparation manufacturing)	Repackaging into large and small containers	Liquid Contact	Dermal	Workers	Yes	The potential for dermal exposure to workers exists during import, but exposure will only occur in the event the imported material is repackaged
				Solid Contact	Dermal	Workers	Yes	HHCB could be imported as a solid; therefore, dermal exposures for workers are expected
				Vapor	Inhalation	Workers, ONU	Yes	Due to its volatility (VP = 0.000545 mmHg) at room temperature, EPA plans to evaluate inhalation exposure
				Mist	Inhalation/ Dermal	Workers, ONU	No	Mist generation is not expected during import or repackaging
				Dust	Inhalation/ Dermal	Workers, ONU	Yes	HHCB could be imported as a solid; therefore, exposures to dust for workers are expected
				Liquid/Solid Contact	Dermal	ONU	No	Dermal exposure by ONU is not expected for this condition of use as they are not expected to directly handle the chemical.
	Incorporation into formulation, mixture or reaction product	Odor agent (in all other chemical product and preparation manufacturing; miscellaneous manufacturing; soap, cleaning compound, and toilet preparation manufacturing; other: fragrance mixtures and fragrance raw material)	Formulation of soap, cleaning compound, and toilet preparation manufacturing and fragrance mixtures	Liquid Contact	Dermal	Workers	Yes	The potential for dermal exposure to workers exists during formulation
				Solid Contact	Dermal	Workers	Yes	HHCB may be incorporated into a solid or powder; therefore, exposures to solids for workers are expected
				Vapor	Inhalation	Workers, ONU	Yes	Due to its volatility (VP = 0.000545 mmHg) at room temperature, EPA plans to evaluate inhalation pathway
				Mist	Inhalation/ Dermal	Workers, ONU	No	Mist generation not expected during formulation
				Dust	Inhalation/ Dermal	Workers, ONU	Yes	HHCB may be incorporated into a solid or powder; therefore, exposures to dust for workers are expected
				Liquid/Solid Contact	Dermal	ONU	No	Dermal exposure by ONU is not expected for this condition of use as they are not expected to directly handle the chemical
	Incorporation into Article	Odor agent (in plastics material and resin manufacturing)	Plastics material and resin manufacturing	Liquid Contact	Dermal	Workers	Yes	The potential for dermal exposure to workers exists during incorporation into articles
				Solid Contact	Dermal	Workers	Yes	HHCB may be incorporated into a solid or powder; therefore, exposures to solids for workers are expected

Life Cycle Stage	Category	Subcategory	Release / Exposure Scenario	Exposure Pathway	Exposure Route	Receptor / Population	Plans to Evaluate	Rationale
				Vapor	Inhalation	Workers, ONU	Yes	Due to its volatility (VP = 0.000545 mmHg) at room temperature, EPA plans to evaluate inhalation pathway
				Mist	Inhalation/ Dermal	Workers, ONU	No	Mist generation not expected during incorporation into articles
				Dust	Inhalation/ Dermal	Workers, ONU	Yes	HHCB may be incorporated into a solid or powder; therefore, exposures to dust for workers are expected
				Liquid/Solid Contact	Dermal	ONU	No	Dermal exposure by ONU is not expected for this condition of use as they are not expected to directly handle the chemical
	Recycling	Recycling	Recycling of HHCB	Liquid Contact	Dermal	Workers	Yes	HHCB is expected to be recycled as a liquid; therefore, dermal exposures for workers are expected
				Solid Contact	Dermal	Workers	No	HHCB is expected to be recycled as a liquid; therefore, exposures to solids for workers are not expected
				Vapor	Inhalation	Workers, ONU	Yes	Due to its volatility (VP = 0.000545 mmHg) at room temperature, EPA plans to evaluate inhalation pathway
				Mist	Inhalation/ Dermal	Workers, ONU	No	Mist generation is not expected during recycling
				Dust	Inhalation/ Dermal	Workers, ONU	No	HHCB is expected to be recycled as a liquid; therefore, exposures to dust for workers are not expected
				Liquid/Solid Contact	Dermal	ONU	No	Dermal exposure by ONU is not expected for this condition of use as they are not expected to directly handle the chemical
Industrial / commercial	Air Care Products	Instant Action Air Fresheners	Aerosol application of scented air freshener	Liquid Contact	Dermal	Workers	Yes	The potential for dermal exposure to workers exists during aerosol air freshener use
				Solid Contact	Dermal	Workers	No	HHCB is used as a liquid in aerosols; therefore, exposures to solids for workers are not expected
				Vapor	Inhalation	Workers, ONU	No	Due to the low volatility (VP = 0.000545 mmHg) of HHCB, inhalation exposures from aerosol applications are expected to be dominated by the aerosol mist, such that exposures to vapors evaporating from the mist droplets does not

Life Cycle Stage	Category	Subcategory	Release / Exposure Scenario	Exposure Pathway	Exposure Route	Receptor / Population	Plans to Evaluate	Rationale
								contribute significantly to HHCB inhalation exposures for this use
				Mist	Inhalation/ Dermal	Workers, ONU	Yes	Mist generation is expected during aerosol application
				Dust	Inhalation/ Dermal	Workers, ONU	No	HHCB is used as a liquid in aerosols; therefore, exposures to dusts are not expected
				Liquid/Solid Contact	Dermal	ONU	No	Dermal exposure by ONU is not expected for this condition of use as they are not expected to directly handle the chemical
		Air fresheners for motor vehicles	Use of solid air freshener	Liquid Contact	Dermal	Workers	Yes	Motor vehicle air fresheners are expected to have liquid residue on a solid, paper substrate
				Solid Contact	Dermal	Workers	No	Although motor vehicle air fresheners are solids, the substrate is a single, continuous solid with liquid fragrance and therefore, exposures to solids for workers are not expected
				Vapor	Inhalation	Workers, ONU	Yes	Due to its volatility (VP = 0.000545 mmHg) at room temperature, EPA plans to evaluate inhalation pathway
				Mist	Inhalation/ Dermal	Workers, ONU	No	Mist generation is not expected during this use
				Dust	Inhalation/ Dermal	Workers, ONU	No	Solid dust exposure is not expected as the product is one single, continuous piece. No powders are expected.
				Liquid/Solid Contact	Dermal	ONU	No	Dermal exposure by ONU is not expected for this condition of use as they are not expected to directly handle the chemical
		Continuous Action Air Fresheners Aroma chemicals	Use of solid/gel room air freshener and fragrance oils	Liquid Contact	Dermal	Workers	Yes	HHCB continuous action air fresheners are typically a solid substrate with a liquid fragrance or a thick gel fragrance mixture; therefore, liquid dermal exposures for workers are expected
				Solid Contact	Dermal	Workers	No	Although some continuous air fresheners are solids, the substrate is a single, continuous solid with liquid/gel fragrance and therefore, exposures to solids for workers are not expected

Life Cycle Stage	Category	Subcategory	Release / Exposure Scenario	Exposure Pathway	Exposure Route	Receptor / Population	Plans to Evaluate	Rationale
				Vapor	Inhalation	Workers, ONU	Yes	Due to its volatility (VP = 0.000545 mmHg) at room temperature, EPA plans to evaluate inhalation pathway
				Mist	Inhalation/ Dermal	Workers, ONU	No	Mist generation is not expected during this use
				Dust	Inhalation/ Dermal	Workers, ONU	No	HHCB continuous action air fresheners do not contain dusts; therefore, exposures to dust for workers are not expected
				Liquid/Solid Contact	Dermal	ONU	No	Dermal exposure by ONU is not expected for this condition of use as they are not expected to directly handle the chemical
			Use of scented candles	Liquid Contact	Dermal	Workers	No	Candles are solids, therefore, exposures to liquids for workers is not expected
				Solid Contact	Dermal	Workers	Yes	Candles are solids, therefore, exposures to solids for workers is expected
				Vapor	Inhalation	Workers, ONU	Yes	Due to its volatility (VP = 0.000545 mmHg) at room temperature, EPA plans to evaluate inhalation pathway
				Mist	Inhalation/ Dermal	Workers, ONU	No	Mist generation is not expected during this use
				Dust	Inhalation/ Dermal	Workers, ONU	No	HHCB continuous action air fresheners do not contain dusts; therefore, exposures to dust for workers are not expected
				Liquid/Solid Contact	Dermal	ONU	No	Dermal exposure by ONU is not expected for this condition of use as they are not expected to directly handle the chemical
	Cleaning and Furnishing Care Products	Cleaning products, including all-purpose liquid cleaner and bathroom cleaners (liquid, , foam, spray, and	Spray application of cleaners and deodorizers (such as multi-surface cleaners and bathroom cleaners)	Liquid Contact	Dermal	Workers	Yes	HHCB is used as a liquid in sprays; therefore, dermal exposures for workers are expected
				Solid Contact	Dermal	Workers	No	HHCB is used as a liquid in sprays; therefore, exposures to solids for workers are not expected
				Vapor	Inhalation	Workers, ONU	No	Due to the low volatility (VP = 0.000545 mmHg) of HHCB, inhalation exposures from aerosol applications are expected to be dominated by the aerosol mist, such that exposures to vapors evaporating from the mist droplets does not

Life Cycle Stage	Category	Subcategory	Release / Exposure Scenario	Exposure Pathway	Exposure Route	Receptor / Population	Plans to Evaluate	Rationale
		powder cleaners)						contribute significantly to HHCB inhalation exposures for this use
				Mist	Inhalation/ Dermal	Workers, ONU	Yes	Mist generation is expected during spray application
				Dust	Inhalation/ Dermal	Workers, ONU	No	HHCB is used as a liquid in sprays; therefore, exposures to dusts are not expected
				Liquid/Solid Contact	Dermal	ONU	No	Dermal exposure by ONU is not expected for this condition of use as they are not expected to directly handle the chemical
			Application of liquid cleaners (such as floor cleaners and hard-surface cleaners)	Liquid Contact	Dermal	Workers	Yes	HHCB is used as a liquid; therefore, dermal exposures for workers are expected
				Solid Contact	Dermal	Workers	No	HHCB is used as a liquid; therefore, exposures to solids for workers are not expected
				Vapor	Inhalation	Workers, ONU	Yes	Due to its volatility (VP = 0.000545 mmHg) at room temperature, EPA plans to evaluate inhalation pathway
				Mist	Inhalation/ Dermal	Workers, ONU	No	Mist generation is not expected during this use
				Dust	Inhalation/ Dermal	Workers, ONU	No	HHCB is used as a liquid; therefore, exposures to dust for workers are not expected
				Liquid/Solid Contact	Dermal	ONU	No	Dermal exposure by ONU is not expected for this condition of use as they are not expected to directly handle the chemical
			Application of powder cleaners and deodorizers (such as hard surface cleaners and carpet and room deodorizers)	Liquid Contact	Dermal	Workers	No	HHCB cleaning powders are solids; therefore, dermal exposures for workers are not expected
				Solid Contact	Dermal	Workers	Yes	HHCB cleaning powders are solids; therefore, exposures to solids for workers are expected
				Vapor	Inhalation	Workers, ONU	No	EPA plans to evaluate inhalation pathway through dust exposure
				Mist	Inhalation/ Dermal	Workers, ONU	No	Mist generation is not expected during this use
				Dust	Inhalation/ Dermal	Workers, ONU	Yes	Solid dust exposure is expected as the products are powders

Life Cycle Stage	Category	Subcategory	Release / Exposure Scenario	Exposure Pathway	Exposure Route	Receptor / Population	Plans to Evaluate	Rationale
				Liquid/Solid Contact	Dermal	ONU	No	Dermal exposure by ONU is not expected for this condition of use as they are not expected to directly handle the chemical
	Laundry and Dishwashing Products	Laundry products, including liquid laundry detergent and fabric softener	Application of liquid laundry detergent, fabric softener	Liquid Contact	Dermal	Workers	Yes	HHCB is used as a liquid; therefore, exposures to solids for workers are not expected
				Solid Contact	Dermal	Workers	No	HHCB is used as a liquid; therefore, exposures to solids for workers are not expected
				Vapor	Inhalation	Workers, ONU	Yes	Due to its volatility (VP = 0.000545 mmHg) at room temperature, EPA plans to evaluate inhalation pathway
				Mist	Inhalation/ Dermal	Workers, ONU	No	Mist generation is not expected during this use
				Dust	Inhalation/ Dermal	Workers, ONU	No	HHCB is used as a liquid; therefore, exposures to dust for workers are not expected
				Liquid/Solid Contact	Dermal	ONU	No	Dermal exposure by ONU is not expected for this condition of use as they are not expected to directly handle the chemical
			Application of solid laundry detergent	Liquid Contact	Dermal	Workers	No	HHCB washing powders are solids; therefore, dermal exposures for workers are not expected
				Solid Contact	Dermal	Workers	Yes	HHCB washing powders are solids; therefore, exposures to solids for workers are expected
				Vapor	Inhalation	Workers, ONU	No	EPA plans to evaluate inhalation pathway through dust exposure
				Mist	Inhalation/ Dermal	Workers, ONU	No	Mist generation is not expected during this use
				Dust	Inhalation/ Dermal	Workers, ONU	Yes	Solid dust exposure is expected as the products are powders
				Liquid/Solid Contact	Dermal	ONU	No	Dermal exposure by ONU is not expected for this condition of use as they are not expected to directly handle the chemical
	Plastic and Rubber Products	Plastic and rubber products	Interaction with plastic and rubber packaging	Liquid Contact	Dermal	Workers	No	HHCB plastic and rubber packagings are solids; therefore, dermal exposures for workers are not expected
				Solid Contact	Dermal	Workers	Yes	HHCB plastic and rubber packagings are solids; therefore, exposures to solids for workers are expected

Life Cycle Stage	Category	Subcategory	Release / Exposure Scenario	Exposure Pathway	Exposure Route	Receptor / Population	Plans to Evaluate	Rationale
				Vapor	Inhalation	Workers, ONU	No	EPA plans to evaluate inhalation pathway through dust exposure
				Mist	Inhalation/ Dermal	Workers, ONU	No	Mist generation is not expected during this use
				Dust	Inhalation/ Dermal	Workers, ONU	No	No dust exposure is expected as the HHCB in the product will be entrained in the packaging and not handled in a way that will result in dust generation (*e.g.*, it will not be cut or sawed)
				Liquid/Solid Contact	Dermal	ONU	No	Dermal exposure by ONU is not expected for this condition of use as they are not expected to directly handle the chemical
	Other Uses	Laboratory Chemicals	Worker handling HHCB	Liquid Contact	Dermal	Workers	Yes	HHCB is used as a liquid; therefore, exposures to solids for workers are not expected
				Solid Contact	Dermal	Workers	No	HHCB is used as a liquid; therefore, exposures to solids for workers are not expected
				Vapor	Inhalation	Workers, ONU	Yes	Due to its volatility (VP = 0.000545 mmHg) at room temperature, EPA plans to evaluate inhalation pathway
				Mist	Inhalation/ Dermal	Workers, ONU	No	Mist generation is not expected during this use
				Dust	Inhalation/ Dermal	Workers, ONU	No	HHCB is used as a liquid; therefore, exposures to dust for workers are not expected
				Liquid/Solid Contact	Dermal	ONU	No	Dermal exposure by ONU is not expected for this condition of use as they are not expected to directly handle the chemical
Disposal	Waste Handling, Treatment and Disposal	Disposal of HHCB wastes	Worker handling of wastes	Liquid Contact	Dermal	Workers	Yes	The potential for dermal exposure to workers exists during this use as both liquid and solid formulations may be disposed
				Solid Contact	Dermal	Workers	Yes	The potential for dermal exposure to workers exists during this use as both liquid and solid formulations may be disposed
				Vapor	Inhalation	Workers, ONU	Yes	Due to its volatility (VP = 0.000545 mmHg) at room temperature, EPA plans to evaluate inhalation pathway
				Mist	Inhalation/ Dermal	Workers, ONU	No	Mist generation is not expected during this use

Life Cycle Stage	Category	Subcategory	Release / Exposure Scenario	Exposure Pathway	Exposure Route	Receptor / Population	Plans to Evaluate	Rationale
				Dust	Inhalation/ Dermal	Workers	Yes	HHCB solid waste may create solid dust during disposal
				Dust	Inhalation/ Dermal	ONU	No	Dermal exposure by ONU is not expected for this condition of use as they are not expected to directly handle the chemical
				Liquid/Solid Contact	Dermal	ONU	No	Dermal exposure by ONU is not expected for this condition of use as they are not expected to directly handle the chemical

Appendix G SUPPORTING INFORMATION – CONCEPTUAL MODEL FOR CONSUMER ACTIVITIES AND USES

Table_Apx G-1. Consumer Exposure Conceptual Model Supporting Table

Life Cycle Stage	Category	Subcategory	Release from Source	Exposure Pathway	Route	Receptor	Plans to Evaluate	Rationale
Consumer Use	Paper Products	Paper Products	Direct contact through application or use of products using HHCB-based products	Liquid (HHCB fragrance oil)	Dermal	Consumers	Yes	Dermal exposure to consumers exists during use as a liquid, and is in scope
			Long-term emission/mass-transfer	Vapor	Inhalation	Consumers and Bystanders	Yes	Due to its volatility (VP = 0.000545 mmHg) at room temperature, inhalation pathway is in scope
Consumer Use	Plastic and Rubber Products	Plastic and Rubber Products	Direct contact through application or use of products using HHCB-based products	Liquid (HHCB fragrance oil)	Dermal	Consumers	Yes	Dermal exposure to consumers exists during use as a liquid, and is in scope
			Long-term emission/mass-transfer	Vapor	Inhalation	Consumers and Bystanders	Yes	Due to its volatility (VP = 0.000545 mmHg) at room temperature, inhalation pathway is in scope
Consumer Use	Air Care Products	Air Care Products	Direct contact through application or use of products using HHCB-based products/	Vapor/Mist	Inhalation	Consumers and Bystanders	Yes	Vapor, and mist generation is expected during aerosol application. Due to its volatility (VP = 0.000545 mmHg) at room temperature, inhalation of vapor and mist pathway is in scope

Life Cycle Stage	Category	Subcategory	Release from Source	Exposure Pathway	Route	Receptor	Plans to Evaluate	Rationale
			Long-term emission/mass-transfer		Dermal	Consumers	Yes	Dermal exposure to consumers exists during use as a spray, and is in scope
Consumer Use	Cleaning and Furnishing Care Products	Cleaning and Furnishing Care Products	Direct contact through application or use of products using HHCB-based products	Liquid	Dermal	Consumers	Yes	Dermal exposure to consumers exists during use as a liquid, and is in scope
			Direct contact through application or use of products using HHCB-based products/ Long-term emission/mass-transfer, Direct Transfer to Dust	Vapor/Mist	Inhalation	Consumers and Bystanders	Yes	Vapor, and mist generation is expected during liquid spray application. Due to its volatility (VP = 0.000545 mmHg) at room temperature, inhalation of vapor and mist pathway is in scope
					Dermal	Consumers	Yes	Dermal exposure to consumers exists during use as a spray, and is in scope
				Dust	Inhalation	Consumers and Bystanders	Yes	Solid dust exposure pathway is expected as during use of powdered soaps containing HHCB, and is in scope
Consumer Use	Laundry and Dishwashing Products	Laundry and Dishwashing Products	Direct contact through application or use of products using HHCB-based products	Liquid	Dermal	Consumers	Yes	Dermal exposure to consumers exists during use as a liquid, and is in scope

Life Cycle Stage	Category	Subcategory	Release from Source	Exposure Pathway	Route	Receptor	Plans to Evaluate	Rationale
			Direct contact through application or use of products using HHCB-based products/ Long-term emission/mass-transfer, Direct Transfer to Dust	Vapor/Mist	Inhalation	Consumers and Bystanders	Yes	Vapor, and mist generation is expected during liquid spray application. Due to its volatility (VP = 0.000545 mmHg) at room temperature, inhalation of vapor and mist pathway is in scope
					Dermal	Consumers	Yes	Dermal exposure to consumers exists during use as a spray, and is in scope
				Dust	Inhalation	Consumers and Bystanders	Yes	Solid dust exposure pathway is expected as during use of powdered detergents containing HHCB, and is in scope

Appendix H SUPPORTING INFORMATION – CONCEPTUAL MODEL FOR ENVIRONMENTAL RELEASES AND WASTES

Table_Apx H-1. General Population and Environmental Exposure Conceptual Model Supporting Table

Life Cycle Stage	Category	Release	Exposure Pathway / Media	Exposure Routes	Receptor / Population	Plans to Evaluate	Rationale
All	Emissions to Air	Emissions to Air	Near facility ambient air concentrations	Inhalation	General Population	Yes	HHCB deposition to nearby bodies of water and soil are expected exposure pathways, not covered under other EPA regulations, and, therefore in scope.
			Indirect deposition to nearby bodies of water and soil catchments	Oral Dermal	General Population	Yes	
				TBD	Aquatic and Terrestrial Receptors	Yes	
	Wastewater or Liquid Wastes	Industrial pre-treatment and wastewater treatment, or POTW	Direct release into surface water and indirect partitioning to sediment	TBD	Aquatic and Terrestrial Receptors	Yes	Release of HHCB into surface water and indirect partitioning to sediment exposure pathways to aquatic and terrestrial receptors is in scope
				Oral Dermal	General Population	Yes	Release of HHCB into surface water and indirect partitioning to sediment and bioaccumulation exposure pathways to the general population is in scope.
			Drinking Water via Surface or Ground Water	Oral Dermal and Inhalation (*e.g.* showering)	General Population	Yes	Release of HHCB into surface water and indirect partitioning to drinking water is in scope.
			Biosolids: application to soil and/or migration to groundwater and/or surface water	Oral (*e.g.* ingestion of soil) Inhalation	General Population	Yes	EPA plans to analyze the pathway from biosolids to the general population, aquatic species, and terrestrial species.
				TBD	Aquatic and Terrestrial Receptors	Yes	
Disposal	Solid and Liquid Wastes	Municipal landfill and other land disposal	Leachate to soil, ground water and/or mitigation to surface water	Oral Dermal	General Population	Yes	EPA plans to analyze the pathway from municipal landfills and other land disposal to the general population, aquatic and terrestrial receptors.
				TBD	Aquatic and Terrestrial Receptors		