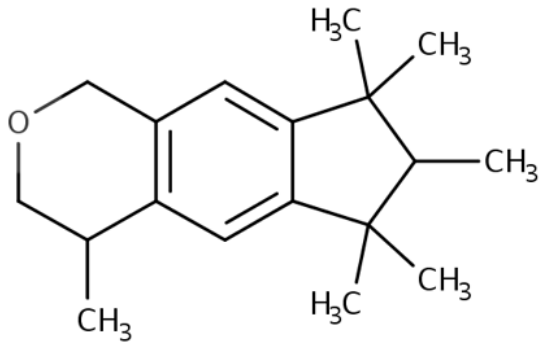
United States
Environmental Protection Agency

March 2026
Office of Chemical Safety and
Pollution Prevention

Draft Ethics Reviews for Intentional Human Dosing Studies for 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[γ]-2-benzopyran (HHCB)

Support Document for the Draft Risk Evaluation

CASRN 1222-05-5



March 2026

1 Introduction

This supplemental file contains ethics reviews for human health hazard studies involving intentional human dosing. These studies are discussed in the *Draft Human Health and Environmental Hazard Assessment for 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[γ]-2-benzopyran (HHCB)* (U.S. EPA, 2026). Table 1 lists these studies in the order that they are reviewed.

Table 1. Studies Reviewed in this Supplement

Number	Title	Reference
1	Fragrance contact dermatitis: a worldwide multicenter investigation (Part II)	(Larsen et al., 2001)
2	Fragrance contact dermatitis in Korea: a joint study	(An et al., 2005)
3	HHCB no. 24. Repeated insult patch test (sanitized) Repeated patch test. Galaxolide. (sanitized) Repeated insult patch test galaxolide 50. (sanitized)	(IFF, 1973a) (IFF, 1964) (IFF, 1973b)

References

An, SS; Lee, AY; Lee, CH; Kim, DW; Hahm, JH; Kim, KJ; Moon, KC; Won, YH; Ro, YS; Eun, HC. (2005). Fragrance contact dermatitis in Korea: a joint study. Contact Derm 53: 320-323. https://dx.doi.org/10.1111/j.0105-1873.2005.00720.x

IFF. (1964). Repeated patch test. Galaxolide. (sanitized). New York, NY.

IFF. (1973a). HHCB no. 24. Repeated insult patch test (sanitized). New York, NY: International Flavors & Fragrances ::IFF.

IFF. (1973b). Repeated insult patch test galaxolide 50. (sanitized). New York, NY: International Flavors & Fragrances :: IFF.

Larsen, W; Nakayama, H; Fischer, T; Elsner, P; Frosch, P; Burrows, D; Jordan, W; Shaw, S; Wilkinson, J; Marks, J; Sugawara, M; Nethercott, M; Nethercott, J. (2001). Fragrance contact dermatitis: a worldwide multicenter investigation (Part II). Contact Derm 44: 344-346. https://dx.doi.org/10.1034/j.1600-0536.2001.044006344.x

U.S. EPA. (2026). Draft Human Health and Environmental Hazard Assessment for 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[γ]-2-benzopyran (HHCB). Washington, DC: Office of Pollution Prevention and Toxics.

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

WASHINGTON, D.C. 20460

August 1, 2025

MEMORANDUM

SUBJECT: Ethics Review of "Fragrance contact dermatitis: a worldwide multicenter investigation"

FROM: Michelle Arling
Human Research Ethics Review Officer
Office of Pesticide Programs

MICHELLE ARLING
Digitally signed by MICHELLE ARLING
Date: 2026.03.11 11:30:00 -04'00'

TO: Rochelle Bohaty
Existing Chemicals Risk Assessment Division
Office of Pollution Prevention and Toxics

The Office of Pollution Prevention and Toxics has requested that I review the ethical conduct of the research described in the article "Fragrance contact dermatitis: a worldwide multicenter investigation (Part II)", published in Contact Dermatology, Volume 44, 2001. I have completed an ethics review of the human research portion of the referenced document. I defer to others for a review of the scientific validity of the study. If the study is not valid, it would not be ethical to rely on it.

In this study, "178 volunteers were patch tested over a 3-month period in 8 centers in Japan, Northern Ireland, United States, England, Switzerland, and Sweden. All of the volunteers had proven sensitization to fragrance materials established by previous patch tests to fragrance allergens. The majority were drawn from the clinical practices of the participating investigators" (p. 344). Twenty control subjects were also enrolled. The study used accepted patch test methods, applying the substance and re-examining the sites at 2-3 days for the first reading and conducting the second reading 2-5 days after the first.

Summary Assessment of Ethical Conduct of the Research

1. **Value of the Research to Society**: The stated purpose of this research was to test "select fragrance materials in an effort to discover new fragrance allergens and also to define fragrance materials safe for use in cosmetics" (p. 344). The article notes that "contact allergy to fragrance materials is the most common cause of contact dermatitis due to cosmetics" (p. 344). The research has societal value in reducing the incidence of fragrance

sensitization.

2. **Subject Selection**: The article notes that "all volunteers had proven sensitization to fragrance materials established by previous patch tests to fragrance allergens. The majority were drawn from the clinical practices of the participating investigators" (p. 344). An additional 20 control subjects without clinical evidence of fragrance allergy were recruited to prove that the concentrations of the tested substances were subirritant.

3. **Risks and Benefits**: The article does not discuss the risks associated with participation study. In addition to the test subjects, 20 control subjects were in enrolled, who had a risk of becoming sensitized to the test substances. This risk was mitigated by testing to find a sub-irritant dose of the substances rather than the dose at which sensitization could occur.

   There is insufficient information on the risks to study participants and whether they were effectively minimized to allow a determination that the benefits of the study outweighed the risks.

4. **Independent Ethics Review**: There is no information about independent ethics review in the article.

5. **Informed Consent**: There is no information about consent in the article.

6. **Respect for Potential and Enrolled Subjects**: Subjects' privacy was not compromised in the published article. The study protocol included screening to ensure that subjects were healthy and did not have any conditions that could be exacerbated by their participation.

Applicable Standards

The study was conducted in the 1990s in 6 countries, including the United States. The prevailing ethical standards include the 1989 Declaration of Helsinki and the Nuremberg Code (1947). The Declaration of Helsinki underwent a number of revisions through 2013. Some of the key principles from the 1989 Declaration of Helsinki are:

1. Research must be scientifically sound and conducted by qualified personnel.
2. There must be a clear purpose and protocol, reviewed and approved by an independent ethics committee.
3. The importance of the study's objective must outweigh the inherent risks to subjects, and measures to minimize risks must be implemented. The interests of science and society should never take precedence over considerations related to the well-being of the subject.
4. Respect the privacy of subjects and confidentiality of their personal information.
5. Participants should give prior, informed, voluntary consent and have the freedom to withdraw from the study.

Some key principles of the Nuremberg code are: participation must be voluntary, and the subjects must be informed of the nature, duration, and purpose of the test and hazards reasonably expected; the research must avoid unnecessary physical and mental suffering; the benefits must outweigh risks;

and subjects must have freedom to withdraw.

The U.S. Department of Health and Human Services (HHS) and the U.S. Food and Drug Administration (FDA) adopted updated regulations for the protection of human subjects in research and clinical investigations in 1981. These regulations covered informed consent of subjects and protections for the rights and welfare of human subjects involved in research subject to these agencies' jurisdictions. While the research submitted did not cite to these standards, it is reasonable to apply the ethical standards of the 1981 amendments to this study as many institutional review boards followed these standards regardless of the research being reviewed. The rule requires review of proposed research and establishes criteria for approval of such research: risks to subjects must be minimized and reasonable in relation to anticipated benefits (to subjects and/or to resulting knowledge), equitable subject selection, documented informed consent from participants, protection of subjects' privacy and confidential data, and additional safeguards to protect vulnerable subjects.

Although there may be gaps in the documentation of the ethical conduct of human research, deficient documentation does not itself constitute evidence that the ethical conduct of the study was deficient relative to the standards prevailing when the research was conducted.

Compliance with Applicable Standards

Subjects were monitored on a regular basis throughout the study period. All subjects' information was kept confidential; their identities were not revealed in the published article.

Based on the research's conduct in part in the United States, it is reasonable to assume that the protocol was reviewed by an independent ethics committee, that subjects gave written informed consent, and that that the risk to the subjects were minimized and reasonable in light of the expected knowledge to be gained.

Conclusion

Given this information and the absence of any information suggesting that the research was fundamentally unethical or intended to harm participants, I cannot identify a barrier to relying on this research from an ethics perspective. I defer to others for a full review of the scientific validity of this study. If it were determined not to have scientific validity, it would also not be ethically acceptable.

cc: Anna Lowit

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

WASHINGTON, D.C. 20460

February 24, 2026

MEMORANDUM

SUBJECT: Ethics Review of "Fragrance contact dermatitis in Korea: a joint study"

FROM: Lillie Barnett
Existing Chemicals Risk Assessment
Division Office of Pollution Prevention and Toxics

LILLIE MARIE BARNETT Digitally signed by LILLIE MARIE BARNETT Date: 2026.03.11 15:17:19 -04'00'

TO: Rochelle Bohaty
Existing Chemicals Risk Assessment Division
Office of Pollution Prevention and Toxics

The Office of Pollution Prevention and Toxics has requested that I review the ethical conduct of the research described in the article "Fragrance contact dermatitis in Korea: a joint study", published in Contact Dermatitis, Volume 53, 2005. I have completed an ethics review of the human research portion of the referenced document. I defer to others for a review of the scientific validity of the study. If the study is not valid, it would not be ethical to rely on it.

In this study, "422 patients with suspected contact allergy who visited hospitals over the period April 2002 to June 2003 were patch tested over the period in 9 university hospitals in Korea" (p. 320). Twenty control subjects were also enrolled. The study used accepted patch test methods. Specifically, although the schedule of when each test substance was applied and when sites were read was not provided, "Finn Chambers on Scanpor fape tape was used for patch testing, and the results were evaluated according to the recommendation of the International Contact Dermatitis Research Group" (p. 321).

Summary Assessment of Ethical Conduct of the Research

1. **Value of the Research to Society**: The stated purpose of this research was to "determine the frequency of responses to selected fragrances in patients with suspected fragrance

allergy and to evaluate the risk factors" (p. 320). The article notes that "Fragrance sensitization is a significant clinical problem and contact allergy to fragrances is the most common cause of contact dermatitis due to cosmetics" (p. 320). The research has societal value in reducing the incidence of fragrance sensitization.

2. **Subject Selection**: The article notes that "9 dermatology departments of university hospitals and 1 cosmetic company participated in this study. 422 patients with suspected contact allergy who visited the hospitals over the period April 2002 to June 2003 were patch-tested in 9 university hospitals in Korea" (p. 320).

3. **Risks and Benefits**: The article does not discuss the risks associated with participation study or measures taken to mitigate any risk.

   There is insufficient information on the risks to study participants and whether they were effectively minimized to allow a determination that the benefits of the study outweighed the risks.

4. **Independent Ethics Review**: There is no information about independent ethics review in the article.

5. **Informed Consent**: There is no information about consent in the article.

6. **Respect for Potential and Enrolled Subjects**: Subjects' privacy was not compromised in the published article. The study protocol did not mention any screening to ensure that subjects were healthy and did not have any conditions that could be exacerbated by their participation.

Applicable Standards

The study was conducted between April 2002 and June 2003 at 9 university hospitals in Korea. The prevailing ethical standards include the 2000 Declaration of Helsinki and the Nuremberg Code (1947). The Declaration of Helsinki underwent a number of revisions through 2024. Some of the key principles from the 2000 Declaration of Helsinki are:

1. Research must be scientifically sound and conducted by qualified personnel.
2. There must be a clear purpose and protocol, reviewed and approved by an independent ethics committee.
3. The importance of the study's objective must outweigh the inherent risks to subjects, and measures to minimize risks must be implemented. The interests of science and society should never take precedence over considerations related to the well-being of the subject.
4. Respect the privacy of subjects and confidentiality of their personal information.
5. Participants should give prior, informed, voluntary consent and have the freedom to withdraw from the study.

Some key principles of the Nuremberg code are: participation must be voluntary, and the subjects must be informed of the nature, duration, and purpose of the test and hazards reasonably expected; the research must avoid unnecessary physical and mental suffering; the benefits must outweigh risks; and subjects must have freedom to withdraw.

Although there may be gaps in the documentation of the ethical conduct of human research, deficient documentation does not itself constitute evidence that the ethical conduct of the study was deficient relative to the standards prevailing when the research was conducted.

Compliance with Applicable Standards

Subjects were monitored on a regular basis throughout the study period. All subjects' information was kept confidential; their identities were not revealed in the published article.

The research was conducted at the dermatology departments of university hospitals in South Korea. The testing was conducted as an addition to the Korean standard series, primarily in patients who were already being tested for suspected contact allergies. Based on the research's conduct at university hospitals, it is reasonable to expect that the research was conducted and overseen by medical personnel, that it went through a required ethics review process at the university level, that subjects gave written informed consent, and that that the risk to the subjects were minimized and reasonable in light of the expected knowledge to be gained. There is no evidence that the research was fundamentally unethical or deficient relative to the ethical standards in place at the time the research was conducted.

Conclusion

Given this information and the absence of any information suggesting that the research was fundamentally unethical or intended to harm participants, I cannot identify a barrier to relying on this research from an ethics perspective. I defer to others for a full review of the scientific validity of this study. If it were determined not to have scientific validity, it would also not be ethically acceptable.

cc: Anna Lowit
Michelle Arling

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

WASHINGTON, D.C. 20460

January 8, 2026

MEMORANDUM

SUBJECT: Ethics Review of Three Unpublished Human Repeated Insult Patch Test Reports

FROM: Lillie Barnett
Existing Chemicals Risk Assessment Division
Office of Pollution Prevention and Toxics

LILLIE MARIE BARNETT Digitally signed by LILLIE MARIE BARNETT Date: 2026.03.11 15:24:32 -04'00'

TO: Rochelle Bohaty
Existing Chemicals Risk Assessment Division
Office of Pollution Prevention and Toxics

REF: International Flavors & Fragrances (IFF R&D). Repeated Insult Patch Test of Group No. [Redacted]. Unpublished. 1973. (HERO ID 8785146)

International Flavors & Fragrances, Inc. Repeated Insult Patch Test of [Redacted]. Unpublished. 1964. (HERO ID 8785221)

International Flavors & Fragrances (IFF R&D). Repeated Insult Patch Test of Group No. [Redacted]. Unpublished. 1973. (HERO ID 8785659)

I have completed an ethics review of the referenced documents. My findings are below. I defer to others for a review of the scientific validity of the study.

Summary of the Research

The reports describe research conducted to evaluate the primary irritation and sensitization properties of the test substance (galaxolide, also known as HHCB) in three repeated insult patch tests on human panelists. According to the first study report (HERO ID 8785146), test patches (consisting of 0.5 mL of neat galaxolide applied to a 1 x 1-inch Webril swatch affixed to the center of a 1 x 2-inch elastic bandage) were applied to the upper arms of 42 panelists (40 female and 2 male).

According to the second study report (HERO ID 8785221), test patches (consisting of 0.5 mL of 3.75% galaxolide diluted in alcohol SDA 39C applied to a 1 x 1-inch Webril swatch affixed to the center of a 1 x 3-inch elastic bandage) were applied to the upper arms of 40 panelists (28 female and 12 male). The report mentions that "closed" (rather than the previously described "semi-open patches") were used for the first 3 applications for four subjects. While the other two reports did not mention where subjects were recruited from, this report stated that "subjects were furnished by churches, Parent-Teachers Associations, and similar organizations in suburban areas around [location redacted]".

According to the third study report (HERO ID 8785659), test patches (consisting of 0.5 mL of 50% galaxolide diluted in alcohol SDA 39C or 0.5 mL alcohol SDA 39C applied to a 1 x 1-inch Webril swatch affixed to the center of a 1 x 2-inch elastic bandage) were applied to the upper arms of 43 panelists (36 female and 7 male). Each patch was applied to the same area each time unless the severity of a reaction made this inadvisable.

For all three studies, panelists were instructed to remove the patches 24 hours after application and reaction sites were scored. This was repeated for a total of 9 applications. After this, a final (10^{th}) 24-hour challenge application occurred in which duplicate patches were applied, one to the original site and one to a skin site which had not previously received any patches. These studies were sponsored by International Flavors and Fragrances (IFF), in cooperation with an undisclosed laboratory that conducted the studies.

Summary Assessment of Ethical Conduct of the Research

1. **Value of the Research to Society**: The stated purpose of this pre-rule research was "to evaluate the primary irritation and sensitization properties of the test sample in a repeated insult patch test on human panelists." The study results provide evidence regarding whether exposure to galaxolide causes dermal irritation and/or sensitization in humans. EPA proposes to use this information as part of the weight of evidence regarding dermal toxicity in the TSCA risk evaluation for 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta [g]-2-benzopyran (HHCB) (also known as galaxolide).

2. **Subject Selection**: HERO ID 8785146 involved 42 human subjects (40 female and 2 male). HERO ID 8785659 involved 43 human subjects (36 female and 7 male). HERO ID 8785221 involved 43 human subjects (36 female and 7 male) and mentioned that "subjects were furnished by churches, Parent-Teachers Associations, and similar organizations in suburban areas around [location redacted]". There is no further information in the report about how subject selection occurred.

3. **Risks and Benefits**: The doses of galaxolide used in the studies were 100% (neat), 50% (diluted in alcohol SDA 39C), and 3.75% (diluted in alcohol SDA 39C) in a total volume of 0.5 mL. There is no information about how the dose for humans was selected. There is no discussion in the article about the risks or benefits to human subjects.

4. **Independent Ethics Review**: The article does not contain any information about independent ethics review of the research.

5. **Informed Consent**: The article does not contain any information about whether the human subjects gave informed consent to participate in the research.

6. **Respect for Potential and Enrolled Subjects**: Information about the subjects' identities was not revealed in the article. The article does not provide any information about whether the subjects were compensated for their participation in the study.

Requesting Additional Ethics Information

The sponsor, International Flavors and Fragrances, Inc. (IFF), provided documentation of its efforts to obtain documentation related to the ethical conduct of the study. (Attachment 1) IFF attempted to contact the (un-named) organization that currently owns the lab where the studies were conducted in the 1960s and 70s. The organization was unable to obtain any information related to the ethical conduct of the study.

There is no clear and convincing evidence that the conduct of the research was fundamentally unethical or that it was significantly deficient relative to the ethical standards prevailing at the time the research was conducted in a way that placed participants at increased risk of harm or impaired their informed consent. There is no clear evidence in the information available from the study reports that the research was intended to harm participants, or that it was fundamentally unethical in other ways. Although there are gaps in the documentation of the ethical conduct of this research, such gaps are not uncommon in studies conducted during this time period. Deficient documentation does not itself constitute evidence that the ethical conduct of the study was deficient relative to the standards prevailing when it was conducted. I find no evidence that this research was fundamentally unethical, or that its conduct was significantly deficient relative to standards prevailing when it was conducted.

Conclusion

Based on the review of the available information, I find no barrier in law or regulation to EPA reliance on this research. I defer to others for a review of the scientific validity of the study; if it were determined not to have scientific validity, it would also not be ethically acceptable.

cc: Anna Lowit
Michelle Arling

Attachment
Documentation from IFF

Attachment 1: Documentation from IFF

From: Xiao Huang <xiao.huang@iff.com>
Sent: Thursday, September 11, 2025 10:09 PM
To: Putt, Jeffrey <putt.jeffrey@epa.gov>
Subject: RE: EPA - Questions pertaining to certain studies

Internal

Hi Jeffrey,
Thank you for your email.
I received both attachments and was able to identify all three studies you referenced.

We've reached out to the organization that currently owns the lab where the three HRIPTs were conducted in the 1960s–70s. However, given the age of these studies (over 50 years old), we are not optimistic that they will be able to provide the requested documentation.

If the information you're seeking is ultimately unavailable—which seems likely—how would that impact your risk assessment? If helpful, we would be open to conducting a new HRIPT with all required documentation to support your evaluation.

Please let us know how you'd like to proceed.
Thank you again.
Best regards,
Xiao

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