CDER Health Hazard Evaluation

The Incidents, Recalls and Shortages Branch in the Office of Compliance is requesting a health hazard evaluation for a specific product defect described below. Please complete section B.

PLEASE UPLOAD COMPLETED FORM TO DARRTS AND ELECTRONICALLY SIGN AND/OR E-MAIL SIGNED PDF TO cder-OC-recallsandshortages@fda.hhs.gov

Section A (Completed by the Incidents, Recalls and Shortages Branch Staff)

HHE Requester	Lavonia Huff Incidents, Recalls and Shortages Branch (RSB) Division of Supply Chain Integrity (DSCI) Office of Drug Security, Integrity, & Response (ODSIR) Office of Compliance E-mail: Lavonia.huff@fda.hhs.gov Phone: (301) 796-3202
Date of Request	July 7, 2021
Date Evaluation Needed	ASAP
Requested Office	DNPD1
Application Type/Number, if applicable	NA
Product Description	Multiple Aerosol Sunscreen Products (see product list and test results within firms HHE attached)
Product Indication	
Product Labeling	
Firm Information	Johnson and Johnson

Nature of Problem (describe in detail the reason for HHE request, add FAR, MedWatch, analytical data in Appendices)

Firm testing found benzene contamination above ICH and USP limits. Benzene results ranged from 11.2 to 23.6 ppm. Please evaluate the risk to a consumer that would use the product.

Adverse Event Information

Adverse Event Question	**Yes**	**No**
Is CDER Recalls aware of adverse events associated with this product defect?		X

If Yes, provide adverse event information in the section below (e.g. lot/batch number, timeframe associated with the adverse event(s) if known)

(table can expand, character limit TBD)

Section B (Completed by OGD or OND)

Detectability

Detectability Questions	Yes	No
Is the defective product easily identified by a regular user of the product?		X
Is the defective product easily identified by a new user of the product?		X

Rationale for Detectability Selections (Solicit input from OPQ, if applicable)

According to The National Institute for Occupational Safety and Health (NIOSH):[1]
"Benzene has a sweet, aromatic, gasoline-like odor. Most individuals can begin to smell benzene in air at 1.5 to 4.7 ppm. The odor threshold generally provides adequate warning for acutely hazardous exposure concentrations but is inadequate for more chronic exposures."

While benzene has a detectable odor, sunscreens, especially aerosols, can have a variety of odors. For that reason, a consumer who detects the odor of benzene may not identify the product as defective.

Product Intended Use and Labeling *Refer to Appendix for product labeling, indication, dosing, and warnings.*

Is the extent of product use greatest for approved use indications as indicated in the label or for known off-label uses?

Response

Labeled use to prevent sunburn and decrease the risk of skin cancer and early skin aging

Product Consumption

Is use of the **defective** product (i.e., recommended dosing regimen and maximum total daily dose) consistent with dosing recommendations provided in the labeling for the following populations:

- Most likely to use the product?
- Most at risk?

Response (For product mix-ups, please also provide the information for the product with which the mix-up could occur)

[1] Benzene: Systemic Agent. Emergency Response Safety and Health Database. The National Institute for Occupational Safety and Health (NIOSH). Accessed on April 7, 2021 at: https://www.cdc.gov/niosh/ershdb/emergencyresponsecard_29750032.html

Use of the defective sunscreen product is likely consistent with dosing recommendations for individuals most likely to use and most at risk from the product.

Patient Population *Check all that apply*	**Most Likely to Use**	**Most at Risk from product defect**
Infants		X
Children	X	X
Women of child-bearing age	X	X
Pregnant women	X	X
Nursing Mothers	X	X
Immune suppressed individuals	X	X
Special Clinical Situations	X	X
Adults	X	X
Elderly	X	X
Other (describe in rationale below)		X

Provide rationale below for the selection(s) in the table. Within the population most at risk from the defect, could individuals suffering from any conditions or diseases be at more or less risk and, if so, why?

Rationale

Infants are unlikely to use the product because the Drug Facts label states, "Children under 6 months of age: Ask a doctor." and "Keep out of reach of children."

Individuals with altered skin absorption (i.e., infants, elderly, broken skin) and individuals, who are exposed to benzene from other sources (e.g., smokers or occupational/environmental exposure), may be at greater risk.

The Agency for Toxic Substances and Disease Registry (ASDTR) peer review panel for benzene[2] identified risk factors with human data to support increased susceptibility to benzene toxicity:

- Genetic polymorphisms associated with processes related to benzene metabolism
- Medical conditions that include reduced bone marrow function or decreased blood factors
- Ethanol use, which can enhance the hematotoxic effects of benzene

Regarding benzene toxicity in children, the ASDTR peer review panel for benzene did not locate human or animal evidence of age-related differences in susceptibility to benzene toxicity.[3]

[2] Toxicological Profile for Benzene. Agency for Toxic Substances and Disease Registry (ASDTR). 2007. Accessed on 4/8/2021 at: https://www.atsdr.cdc.gov/toxprofiles/tp3.pdf

[3] Toxicological Profile for Benzene. Agency for Toxic Substances and Disease Registry (ASDTR). 2007. Accessed on 4/8/2021 at: https://www.atsdr.cdc.gov/toxprofiles/tp3.pdf

Health Hazard Clinical Assessment

Describe the clinical significance or health implications of the product defect (i.e., adverse health consequences that could occur with use of the product).

Rationale

According to the ICH guideline Q3C (R6) on impurities, there is sufficient evidence to establish that benzene is a human carcinogen (lymphatic and hematopoietic cancers).[4] The ICH assessment says: "From the data of human leukemia and exposure concentrations of benzene, it was calculated that a daily intake of 0.02 mg was associated with a lifetime excess cancer risk of 10^{-5} and provides a guideline value for benzene of 0.02 mg per day (2 ppm)."

The United States Pharmacopeia (USP) Residual Solvents limits the concentration of benzene to not more than 2 parts per million (ppm).[5] For this HHE, an evaluation of the likelihood and risks associated with using aerosol sunscreens that contain benzene 11.2 to 23.6 ppm is requested. These levels exceed the guideline value provided by ICH and USP.

Exposure to benzene can occur via inhalation, oral, and dermal routes.[6] The Drug Facts label contains following information, which may reduce exposure:

- Hold container 4-6 inches from the skin to apply. Rub in.
- Do not spray directly on face. Spray on hands and then apply on face.
- Do not apply in risky conditions.
- Use in a well-ventilated area.
- For external use only.
- Do not use on damaged or broken skin.
- Keep out of eyes. Rinse with water to remove.
- Keep away from face to avoid breathing it.
- If swallowed, get medical help or contact Poison Control Center right away.
- Do not use near fire, or while smoking.
- Intentional misuse by deliberately concentrating and inhaling the content can be harmful or fatal.

The International Agency for Research on Cancer has classified benzene as carcinogenic to humans (Group 1).[7] Benzene causes myelodysplastic syndromes and acute myeloid leukemia. Myelodysplastic syndromes and acute myeloid leukemia exist along a continuous disease spectrum, and myelodysplastic syndromes may progress to acute

[4] ICH guideline Q3C (R6) on impurities – support document 1: toxicological data for class 1 solvents. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). Accessed on 4/8/2021 at: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-q3c-r6-impurities-support-document-1-toxicological-data-class-1-solvents-step-5_en.pdf

[5] United States Pharmacopeia (USP) Residual Solvents. Accessed on 7/8/2021 at: https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/generalChapter467Current.pdf

[6] Toxicological Review of Benzene (Noncancer Effects). EPA Integrated Risk Information System (IRIS). Accessed on 4/8/2021 at: https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0276tr.pdf

[7] Benzene Monograph. The International Agency for Research on Cancer (IARC). Accessed 4/8/2021 at: https://monographs.iarc.who.int/wp-content/uploads/2018/06/mono100F-24.pdf

myeloid leukemia.

There also is limited evidence that benzene may cause acute and chronic lymphocytic leukemia, non-Hodgkin's lymphoma and multiple myeloma. Chronic exposure to benzene has caused various disorders in the blood, including reduced numbers of red blood cells and aplastic anemia.

Additional information regarding benzene is available at the following:

- Environmental Protection Agency: https://www.epa.gov/sites/production/files/2016-09/documents/benzene.pdf
- Occupational Safety and Health Administration: https://www.osha.gov/laws-regs/regulations/standardnumber/1910/1910.1028AppA

Likelihood of Adverse Event Occurring *If more than one choice is selected, please explain*	**Population Most Likely to Use**	**Population Most at Risk from product defect**
Highly likely to occur *Every time the product is used*		
Likely to occur *Reasonable probability*	X	X
Might occur *Remote probability*		
Unlikely to occur		
Unknown *Explain*		

Rationale:

The aerosol sunscreens reviewed contain benzene 11.2 to 23.6 ppm. These levels exceed ICH and USP the guideline value of 2 ppm.

Degree of Health Hazard Associated with Use of Defective Product *If more than one choice is selected, please explain*	**Population Most Likely to Use**	**Population Most at Risk from product defect**
Life-threatening (death has or could occur)	X	X
Could result in permanent impairment of a body function or permanent damage to a body structure	X	X
Necessitates medical or surgical intervention to preclude or reverse permanent damage or impairment of a body structure or function	X	X
Could cause temporary or reversible		

(without medical intervention) adverse health consequences		
Could cause limited adverse health consequences (transient, minor impairment or complaints)		
Not likely to cause adverse health consequences		
Hazard cannot be assessed with the data currently available *Explain*		

Rationale

According to ICH guideline Q3C (R6) on impurities, there is sufficient evidence to establish that benzene is a human carcinogen (lymphatic and hematopoietic cancers). The International Agency for Research on Cancer has classified benzene as carcinogenic to humans.

Signature(s)	Valerie S. Pratt -S Digitally signed by Valerie S. Pratt -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300418583, cn=Valerie S. Pratt -S Date: 2021.07.08 16:12:44 -04'00'
Signature(s)	Nushin Todd -S Digitally signed by Nushin Todd -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Nushin Todd -S, 0.9.2342.19200300.100.1.1=0011364715 Date: 2021.07.08 16:21:08 -04'00'

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HHE for Investigation
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