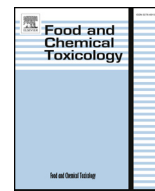




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Short Review

RIFM fragrance ingredient safety assessment, 3-mercaptohexanol, CAS Registry Number 51755-83-0



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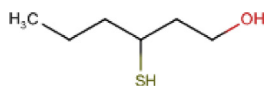
Keywords:

Genotoxicity
Repeated dose, developmental, and reproductive toxicity
Skin sensitization
Phototoxicity/photoallergenicity
Local respiratory toxicity
Environmental safety

Version: 121918. This version replaces any previous versions.

Name: 3-Mercaptohexanol

CAS Registry Number: 51755-83-0



Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration

AF - Assessment Factor

BCF - Bioconcentration Factor

Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 2017) compared to a deterministic aggregate approach

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DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
 DST - Dermal Sensitization Threshold
 ECHA - European Chemicals Agency
 ECOSAR - Ecological Structure-Activity Relationships Predictive Model
 EU - Europe/European Union
 GLP - Good Laboratory Practice
 IFRA - The International Fragrance Association
 LOEL - Lowest Observable Effect Level
 MOE - Margin of Exposure
 MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
 NA - North America
 NESIL - No Expected Sensitization Induction Level
 NOAEC - No Observed Adverse Effect Concentration
 NOAEL - No Observed Adverse Effect Level
 NOEC - No Observed Effect Concentration
 NOEL - No Observed Effect Level
 OECD - Organisation for Economic Co-operation and Development

(RIFM, 2001; RIFM, 2017a)

Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: No safety concerns at current, declared use levels; the exposure is below the DST.
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV Spectra, RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence:

Critical Measured Value: 10% (OECD 301 D) (RIFM (2000a))

Bioaccumulation:

Screening-level: 6.09 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity:

Screening-level: Fish LC50: 602.4 mg/L (RIFM Framework; Salvito et al., 2002)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) < 1 (RIFM Framework; Salvito et al., 2002)

Critical Ecotoxicity Endpoint: Fish LC50: 602.4 mg/L (RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.6024 µg/L

• **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: not applicable; cleared at screening-level

OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines

PBT - Persistent, Bioaccumulative, and Toxic

PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration

QRA - Quantitative Risk Assessment

QSAR - Quantitative Structure-Activity Relationship

REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals

RfD - Reference Dose

RIFM - Research Institute for Fragrance Materials

RQ - Risk Quotient

Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test

TTC - Threshold of Toxicological Concern

UV/Vis spectra - Ultraviolet/Visible spectra

VCF - Volatile Compounds in Food

VoU - Volume of Use

vPvB - (very) Persistent, (very) Bioaccumulative

WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api et al., 2015), which should be referred to for clarifications.

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

Summary: The existing information supports the use of this material as described in this safety assessment.

3-Mercaptohexanol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 3-mercaptohexanol is not genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class I material, and the exposure to 3-mercaptohexanol is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). The skin sensitization endpoint was completed using the DST for reactive materials (64 µg/cm²); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; 3-mercaptohexanol is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 3-mercaptohexanol was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.

1. Identification

- 1. Chemical Name:** 3-Mercaptohexanol
- 2. CAS Registry Number:** 51755-83-0
- 3. Synonyms:** 3-Thiohexanol; 3-Thiohexan-1-ol; 3-Mercaptohexanol
- 4. Molecular Formula:** C₆H₁₄OS
- 5. Molecular Weight:** 134.24
- 6. RIFM Number:** 6783
- 7. Stereochemistry:** No isomer specified. One stereocenter and 2 total stereoisomers possible.

2. Physical data

- 1. Boiling Point:** 244.5 °C at 1009 hPa–245 hPa (RIFM, 2000e)
- 2. Flash Point:** 107.6 °C (RIFM, 2000d)
- 3. Log K_{OW}:** 1.4 at 30 °C (RIFM, 2000c)
- 4. Melting Point:** between -70 °C and -45 °C (203–228K) (RIFM, 2000f)
- 5. Water Solubility:** Not Available
- 6. Specific Gravity:** Not Available
- 7. Vapor Pressure:** 0.0154 mm Hg @ 20 °C (EPI Suite v4.0)
- 8. UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol⁻¹ · cm⁻¹)
- 9. Appearance/Organoleptic:** Not Available

3. Exposure to fragrance ingredient

- 1. Volume of Use (Worldwide Band):** < 0.1 metric ton per year (IFRA, 2015)
- 2. 95th Percentile Concentration in Hydroalcoholics:** 0.0006% (RIFM, 2017b)
- 3. Inhalation Exposure*:** 0.0000035 mg/kg/day or 0.00024 mg/day (RIFM, 2017b)
- 4. Total Systemic Exposure**:** 0.00010 mg/kg/day (RIFM, 2017b)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey et al., 2015; Safford et al., 2015a; Safford et al., 2017; and Comiskey

et al., 2017).

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 4. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015a; Safford et al., 2017; and Comiskey et al., 2017).

4. Derivation of systemic absorption

1. **Dermal:** Assumed 100%
2. **Oral:** Assumed 100%
3. **Inhalation:** Assumed 100%

5. Computational toxicology evaluation

1. **Cramer Classification:** Class I, Low

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
I	I	I

2. **Analogs Selected:**
 - a. Genotoxicity: None
 - b. Repeated Dose Toxicity: None
 - c. Reproductive Toxicity: None
 - d. Skin Sensitization: None
 - e. Phototoxicity/Photoallergenicity: None
 - f. Local Respiratory Toxicity: None
 - g. Environmental Toxicity: None
3. **Read-across Justification:** None

6. Metabolism

No relevant data available for inclusion in this safety assessment.

6.1. Additional References

None.

7. Natural occurrence (discrete chemical) or composition (NCS)

3-Mercaptohexanol is reported to occur in the following foods by the VCF*:

Beer.
Citrus fruits.
Guava and feyoa
Hop (*Humulus lupulus*).
Passion fruit (*Passiflora* species).
Wine.

*VCF Volatile Compounds in Food: Database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. REACH Dossier

Available; accessed 12/19/18 (ECHA, 2012b).

9. Conclusion

The existing information supports the use of this material as

described in this safety assessment.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, 3-mercaptohexanol does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. The mutagenic activity of 3-mercaptohexanol has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538, and TA102 were treated with 3-mercaptohexanol in dimethyl sulfoxide (DMSO) at concentrations up to 5000 µg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2001). Under the conditions of the study, 3-mercaptohexanol was not mutagenic in the Ames test.

The clastogenic activity of 3-mercaptohexanol was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with 3-mercaptohexanol in DMSO at concentrations up to 1340 µg/mL in the dose range finding (DRF) study. Micronuclei analysis was conducted at 750 µg/mL in the presence and absence of metabolic activation (S9) for 3 h and in the absence of metabolic activation for 24 h 3-Mercaptohexanol did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either the presence or absence of an S9 activation system (RIFM, 2017a). Under the conditions of the study, 3-mercaptohexanol was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the available data, 3-mercaptohexanol does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/27/19.

10.1.2. Repeated dose toxicity

There are no repeated dose toxicity data on 3-mercaptohexanol or any read-across materials. The total systemic exposure to 3-mercaptohexanol is below the TTC for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on 3-mercaptohexanol or on any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 3-mercaptohexanol (0.10 µg/kg bw/day) is below the TTC (30 µg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/31/19.

10.1.3. Reproductive toxicity

There are no reproductive toxicity data on 3-mercaptohexanol or on any read-across materials. The total systemic exposure to 3-mercaptohexanol is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

10.1.3.1. Risk assessment. There are no reproductive toxicity data on 3-mercaptohexanol or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 3-mercaptohexanol (0.10 µg/kg bw/day) is below the TTC (30 µg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the

reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/23/19.

10.1.4. Skin sensitization

Based on the existing data, the Expert Panel for Fragrance Safety applied the reactive DST for 3-mercaptohexanol, and it does not present a concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. The chemical structure of this material indicates that it would be expected to react with skin proteins (Roberts et al., 2007; OECD Toolbox v4.2). In a guinea pig maximization test, 3-mercaptohexanol was tested using 5% and 100% and 100% for the intradermal induction, topical induction, and topical challenge. The report concluded that 1/20 animals tested with 3-mercaptohexanol exhibited reactions indicative of skin sensitization. Acting conservatively, due to the insufficient data, the reported exposure was benchmarked utilizing the reactive DST of 64 µg/cm² (Safford, 2008; Safford et al., 2011; Roberts et al., 2015; Safford et al., 2015b). The current exposure from the 95th percentile concentration is below the DST for reactive materials when evaluated in all QRA categories. Table 1 provides the maximum acceptable concentrations for 3-mercaptohexanol that present no appreciable risk for skin sensitization based on the reactive DST. These levels represent maximum acceptable concentrations based on the DST approach. However, additional studies may show it could be used at higher levels.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/28/19.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 3-mercaptohexanol would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for 3-mercaptohexanol in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity

(Henry et al., 2009). Based on the lack of absorbance, 3-mercaptohexanol does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no significant absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol⁻¹ · cm⁻¹ (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/15/19.

10.1.6. Local respiratory toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 3-mercaptohexanol is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on 3-mercaptohexanol. Based on the Creme RIFM Model, the inhalation exposure is 0.00024 mg/day. This exposure is 5833 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/29/19.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 3-mercaptohexanol was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured

Table 1

Maximum acceptable concentrations for 3-mercaptohexanol that present no appreciable risk for skin sensitization based on reactive DST.

IFRA Category ^a	Description of Product Type	Maximum Acceptable Concentrations in Finished Products Based on Reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.0049%	NRU ^b
2	Products applied to the axillae	0.0015%	NRU ^b
3	Products applied to the face using fingertips	0.029%	NRU ^b
4	Fine fragrance products	0.027%	NRU ^b
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.0070%	6.0 × 10 ⁻⁴ %
6	Products with oral and lip exposure	0.016%	NRU ^b
7	Products applied to the hair with some hand contact	0.056%	NRU ^b
8	Products with significant ano-genital exposure	0.0029%	No Data ^c
9	Products with body and hand exposure, primarily rinse-off	0.054%	0.0075%
10	Household care products with mostly hand contact	0.19%	NRU ^b
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	0.11%	No Data ^c
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not restricted	0.0050%

Note: ^aFor a description of the categories, refer to the IFRA/RIFM Information Booklet.

^bNo reported use.

^cFragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, 3-mercaptohexanol was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC < 1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify 3-mercaptohexanol as possibly persistent or bioaccumulative based on its structure and physical-chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent and bioaccumulative and toxic, or very persistent and very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012a). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF \geq 2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical-chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

Based on the current Volume of Use (IFRA, 2015), 3-mercaptohexanol presents no risk to the aquatic compartment in the screening-level assessment.

10.2.3. Key studies

10.2.3.1. Biodegradation. RIFM, 2000b: The ready biodegradability test was conducted according to the OECD 301D method. Biodegradation of 10% was observed after 28 days.

10.2.3.2. Ecotoxicity. RIFM, 2000a: The *Daphnia magna* acute immobilization test was conducted according to the OECD 202 method. The 48-h EC50 was reported to be 8.5 mg/L.

10.2.4. Other available data

3-Mercaptohexanol has been registered for REACH with no additional data at this time.

10.2.5. Risk assessment refinement

Since 3-mercaptohexanol has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in μ g/L).

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (<i>Daphnia</i>)	EC50 (Algae)	AF	PNEC (μ g/L)	Chemical Class
RIFM Framework Screening-level (Tier 1)	<u>602.4</u>			1000000	0.6024	

Exposure information and PEC calculation (following RIFM Framework: Salvito et al., 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	1.4	1.4
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	< 1
Risk Characterization: PEC/PNEC	< 1	< 1

Based on available data, the RQ for this material is < 1. No further assessment is necessary.

The RIFM PNEC is 0.6024 μ g/L. The revised PEC/PNECs for EU and North America are: not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 01/28/19.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** <https://echa.europa.eu/>
- **NTP:** <https://ntp.niehs.nih.gov/>
- **OECD Toolbox**
- **SciFinder:** <https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf>
- **PubMed:** <https://www.ncbi.nlm.nih.gov/pubmed>
- **TOXNET:** <https://toxnet.nlm.nih.gov/>
- **IARC:** <https://monographs.iarc.fr>
- **OECD SIDS:** <https://hvpchemicals.oecd.org/ui/Default.aspx>
- **EPA ACToR:** <https://actor.epa.gov/actor/home.xhtml>
- **US EPA HPVIS:** https://ofmpub.epa.gov/opphpv/public_search_publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** <https://www.google.com>
- **ChemIDplus:** <https://chem.nlm.nih.gov/chemidplus/>

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 05/31/19.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

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