Center for Biocide Chemistries

December 10, 2020

Submitted Electronically

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RE: Comments on Pesticide Registration Review; Draft Human Health and Ecological Risk Assessments for Isothiazolinones, 3(2H)-isothiazolone, 4,5-dichloro-2-octyl (Docket ID: EPA-HQ-OPP-2014-0403)

Dear Mr. Savage:

The American Chemistry Council's (ACC) Center for Biocides Chemistries' (CBC) Isothiazolinones Task Force (Task Force)[1] provides the attached comments to the U.S. Environmental Protection Agency's (EPA or Agency) Pesticide Registration Review; Draft Human Health and Ecological Risk Assessment (DRA) for 3(2H)-isothiazolone, 4,5-dichloro-2-octyl (DCOIT).[2]

As detailed in the attached comments, EPA's Draft Risk Assessment (DRA) is based on incorrect and insufficient data. If EPA applies the best science, most uses of DCOIT will not pose any significant risks. To the extent risks remain, FIFRA § 2(bb) requires EPA to consider the benefits of these products. The Task Force asserts that even in those situations in which EPA finds risks, those risks are far outweighed by the unique and robust benefits provided by these IT biocides.

The Task Force urges EPA to adopt the modifications to its risk assessment methodology set forth in our comments, along with voluntary use rate reductions undertaken by registrants, which generate acceptable risks under most use scenarios EPA considers in its DRA. Where risks remain, the Task Force urges EPA to acknowledge the substantial benefits of DCOIT.

[1] Members of the Isothiazolinones Task Force include Dalian Bio-Chem Company Ltd., DuPont, LANXESS Corporation, Lonza, LLC., Thor Specialties, Inc., and Troy Chemical Corporation.

[2] EPA-HQ-OPP-2014-0403.

The Task Force requests that EPA reissue the DCOIT DRA, incorporating all of the corrections, changes, and information presented in the attached comments. EPA should not proceed with issuing a Proposed Interim Decision or any risk mitigation for DCOIT until the record is corrected and stakeholders are provided another opportunity to comment.

Should you have any questions, please do not hesitate to contact me at Lane_Hochschwender@americanchemistry.com or (202) 249-6722.

Sincerely,

Lane Hochschwender
Manager, Isothiazolinone Task Force

Enclosure

Cc: Anita Pease, Director, Antimicrobials Division
Komal Jain, Executive Director, Center for Biocide Chemistries

Isothiazolinones Task Force Comments on the Draft Human Health and Ecological Risk Assessment of 3(2H)-isothiazolone, 4,5-dichloro-2-octyl
(Docket ID: EPA-HQ-OPP-2014-0403)

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EXECUTIVE SUMMARY

On May 15, 2020, the U.S. Environmental Protection Agency (EPA) issued Draft Risk Assessments (DRA) for several active ingredients that fall within the isothiazolinones (IT) class of chemistries:

- Benzisothiazolin-3-one, 3(2H)-Isothiazolone (BIT),[3]
- 1,2-Benzisothiazol-3(2H)-one,2-butyl (BBIT),[4]
- Methylisothiazolinone/Chloromethylisothiazolinone (MIT/CMIT),[5]
- Octhilinone (OIT),[6] and
- 3(2H)-isothiazolone, 4,5-dichloro-2-octyl- (DCOIT).[7]

Although the isothiazolinones, as a chemical family, have a similar toxicity profile, potency differs substantially between different members of this family. Accordingly, the American Chemistry Council (ACC) Center for Biocides Chemistries' (CBC) Isothiazolinones Task Force (Task Force) is responding to the DRAs separately.

ITs are widely used because they are broad spectrum biocidal active substances, are effective at very low use rates, have good environmental (not persistent, not bioaccumulating, non-toxic) and toxicological profiles (no chronic or systemic effects) when used as intended. ITs are commonly used to control bacteria, fungi, and/or algae in a variety of materials and processes, including paints, household cleaning products, metalworking fluids, textiles, agricultural pesticide formulations (as an inert), leather production, paper mill water systems, cooling water systems, oil recovery injection water, drilling muds and packer fluids and wood treatments. EPA employed models in the DRA that are overly conservative, and the Task Force is concerned that if EPA does not appropriately consider the benefits of ITs, some end use applications will be left without an acceptable preservative solution at the conclusion of the Registration Review process. Without effective preservation, the availability of treated articles will be severely impacted. The Agency must do a holistic assessment that considers benefits and risks for all biocides for a given use to ensure that effective and acceptable solutions will be available after Registration Review.

The primary objective of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) is to ensure that, when applied as instructed, pesticides "will not generally cause unreasonable adverse effects to man or the environment, taking into account the economic…, social and environmental costs and benefits of the use of any pesticide...".[8] In other words, even if pesticide use may entail some risk, there are recognized benefits, and EPA must balance those risks and benefits in the Registration Review decision making process. EPA's DRAs for the ITs did not discuss or
As detailed in these comments, several mistakes were made by EPA when calculating risks. There is also a significant amount of data that was not incorporated into the human health and ecological

[3] EPA-HQ-OPP-2014-0159.

[4] EPA-HQ-OPP-2015-0736.

[5] EPA-HQ-OPP-2013-0605.

[6] EPA-HQ-OPP-2014-0160.

[7] EPA-HQ-OPP-2014-0403.

[8] FIFRA §2(bb), 7 U.S.C. §136(bb).

risk assessments that the Task Force believes is the best science to assess risks from OIT. When considering these errors and the lack of incorporation of existing data, the results of the risk assessment is not accurate and should be conducted again. Thus, the Task Force requests that EPA reissue the OIT DRA, incorporating all of the corrections, changes, and information presented in these comments. EPA should not proceed with issuing a Proposed Interim Decision or any risk mitigation for OIT until the DRA is corrected and stakeholders are provided another opportunity to comment.

A. DCOIT Use Patterns

On September 26, 2017, EPA issued a Generic Data Call-In Notice (GDCI) for DCOIT, which included a request for Product Use Information (875.1700).[9] The Task Force submitted detailed product use information in response to the GDCI on February 14, 2020 (MRID 51386601).

EPA's summary of DCOIT registered uses is presented in Table 3 of the DRA. The Task Force notes that Table 3 is as not comprehensive as the product use information provided by the Task Force. EPA does not address this gap in the DRA, but the Task Force assumes that if the Agency did not address a use pattern, it is because it determined that no risk of concern is presented.

B. Human Health Risk Summary

The principal endpoints of human health concern for DCOIT use are short-term endpoints that are readily observable, i.e., irritation or corrosion of the skin and eyes. Many of the industries that use OIT are well positioned to identify such adverse effects, and, to our knowledge, adverse effects have not been observed. Yet, the results of EPA's assessment would suggest otherwise. If the Agency's assessment is in fact accurate, numerous incidents would be reported. This disparity should be a signal to EPA that its assessment must be reconsidered.

In fact, the Agency notes that there were no human fatalities or major incidents listed for DCOIT in the Office of Pesticide Programs (OPP) Incident Database System (IDS) in the past five years. Only three incidents were reported between 1999 and 2009, with moderate effects (including irritation, burns, eye irritation and nausea) noted.[10] If EPA's DRA was accurate, there would be more incidents reported. Again, if the DCOIT DRA was accurate, there would be more incidents reported.

<u>Residential Risk Summary</u>

The DCOIT DRA identified residential risks of concern via:

- inhalation exposure to paints preserved with DCOIT in airless spray application;
- dermal exposure to paints preserved with DCOIT in airless spray and brush/roller applications;
- dermal exposure to PVC flooring with DCOIT during post application; and
- dermal exposure to children when contacting DCOIT treated decks/playsets.

[9] GDCI-128101-1482.

[10] *See* DCOIT DRA at 11.

The Task Force contends that EPA's assessment of these risks is further flawed because the DCOIT DRA contains the following errors:

- EPA's assumption regarding the quantity of paint that a residential do-it-yourself (DIY) painter applies is not realistic;
- EPA's assumption that 100% of the DCOIT used to treat an article is transferred to the skin is not realistic and does not consider the Standard Operating Procedure (SOP) for Residential Exposure and Risk Assessment for Pesticides (2012).

In addition, the Task Force disagrees with EPA's selection of the POD using the DCOIT inhalation study in the inhalation exposure assessment and the selection of the induction POD for DCOIT in the dermal exposure assessment.

Based on the foregoing, the Task Force calculated revised inhalation and dermal margins of exposure (MOE) for DCOIT, and pursuant to those recalculations, DCOIT passes the risk assessment for all inhalation exposure scenarios. Similarly, DCOIT passes all dermal exposure scenarios except for DCOIT-preserved paint applied by an airless spray applicator and post application DCOIT-exposure to children when contacting decks/playsets.

Occupational Risk Summary

The DCOIT DRA identified occupational risks of concern via:

- inhalation exposure from handling of open pour liquids for paints;
- inhalation exposure from paints preserved with DCOIT in airless spray application;
- inhalation exposure from shipyard painting when a PF 1000 full face air supplied respirator is not used; and
- dermal exposure from handling of open pour liquids for paints and from professional use of paints preserved with DCOIT.

The Task Force contends that EPA's assessment of occupational inhalation and dermal risks is flawed because the DCOIT DRA contains the following errors:

- EPA incorrectly used the total conventional liquid pour dermal and inhalation unit exposures from the Antimicrobial Exposure Assessment Task Force II (AEATF II) liquid pour study (MRID 48917401) to assess the addition of liquid preservatives to a paint manufacturing process; and
- EPA did not consider the use of a head coverings by professional painters in its assessment of risks from the use of airless sprayers.

In addition, the Task Force disagrees with EPA's selection of the POD using the DCOIT inhalation study in the inhalation exposure assessment and the selection of the induction POD for DCOIT in the dermal exposure assessment.

Based on the foregoing, the Task Force calculated revised inhalation and dermal MOEs for DCOIT as detailed in the body of these comment, and pursuant to those recalculations, DCOIT passes the risk assessment for all inhalation exposure scenarios. For dermal exposures to DCOIT, there are

risks of concern handling of open pour liquids preservatives for paints and professional use of airless spray paint applicators.

C. Additional Considerations

Dermal Sensitization Approach

As explained in EPA's Note to Reader in its May 8, 2020, correspondence to commenters, this is the first time the Agency used *in vitro* data to assess dermal sensitization.[11] This is also the first time the Agency has performed quantitative risk assessments for dermal sensitizers. The Task Force disagrees with the Agency's use of the *in vitro* data and the Shiseido artificial neural network (ANN) model. Instead, EPA should use the best data (human studies) that exist for each of the active ingredients.

[11] Office of Chemical Safety and Pollution Prevention, Envt. Prot. Agency. Instructions for Commenting on the Isothiazolinones Risk Assessments and Hazard Characterization of Isothiazolinones in Support of FIFRA Registration Review (May 8, 2020).

Isothiazolinones Task Force Comments on the Draft Human Health and Ecological Risk Assessment of 3(2H)-isothiazolone, 4,5-dichloro-2-octyl
(Docket ID: EPA-HQ-OPP-2014-0403)

I. INTRODUCTION

The American Chemistry Council's (ACC) Center for Biocides Chemistries' (CBC) Isothiazolinones Task Force (Task Force) provides the following comments to the U.S. Environmental Protection Agency's (EPA or Agency) Pesticide Registration Review; Draft Human Health and Ecological Risk Assessment for 3(2H)-isothiazolone, 4,5-dichloro-2-octyl (DCOIT).[12] Organizationally, the comments follow the order of information presented in the Draft Risk Assessment (DRA).

A. DCOIT Use Patterns and Use Rates

On September 26, 2017, EPA issued a Generic Data Call-In Notice (GDCI) for DCOIT, which included a request for Product Use Information (875.1700).[13] The Task Force submitted detailed product use information in response to the GDCI on February 14, 2020 (MRID 51386601).

EPA's summary of DCOIT registered uses is presented in Table 3 of the DRA. The Task Force notes that Table 3 is as not comprehensive as the product use information provided by the Task Force. EPA does not address this gap in the DRA, but the Task Force assumes that if the Agency did not address a use pattern, it is because it determined that no risk of concern is presented.

B. Risk vs. Benefits: FIFRA Mandate

The primary objective of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) is to ensure that, when applied as instructed, pesticides "will not generally cause unreasonable adverse effects to man or the environment, taking into account the economic…, social and environmental costs and benefits of the use of any pesticide...".[14] In other words, even though pesticide use may entail some risk, there are recognized benefits, and EPA must balance those risks and benefits in the Registration Review decision making process.[15] EPA's DRAs for the ITs are directed only at

[12] EPA-HQ-OPP-2014-0403.

[13] GDCI-128101-1482.

[14] FIFRA §2(bb), 7 U.S.C. §136(bb).

[15] The Task Force is aware that for pesticide uses that may result in dietary exposure, the safety standard for registration is set out in section 408 of the Federal Food Drug and Cosmetic Act (FFDCA), requiring a "reasonable certainty that no harm will result" from such residues. 21 U.S.C. §346(a)(2)(i).

the risk component of the evaluation. In those situations where EPA determines there are no risks, i.e. Margins of Exposure (MOEs) are adequate, no consideration of benefits need take place. If, however, EPA determines there are risks, the statute requires EPA to evaluate both risks and benefits to determine whether the statutory standard for registration is met.

If EPA applies the best available science, as set forth in the Task Force's comments below, most uses of ITs will not pose any significant risks. To the extent risks remain, FIFRA § 2(bb) requires EPA to consider the benefits of these products. EPA's regulations governing Registration Review at 40 C.F.R. Part 155 do not expressly provide when in the process the presentation and consideration of information on benefits must be considered. The DRA does not did not discuss or consider the benefits of the ITs, nor does it expressly seek comments on benefits. The Task Force asserts that even in those situations in which EPA finds risks, those risks are far outweighed by the unique and robust benefits provided by IT biocides.

The Task Force has done its best, during the time provided, to compile information on the benefits of IT biocides. That information is included as Appendix A of these comments. The Task Force anticipates further developing benefits information and plans to provide additional information to EPA as it becomes available. The Task Force also understands that users of IT biocides will be submitting comments on the importance of continued availability of IT biocides with use levels that will provide efficacy.

EPA acknowledges the importance of economic and consumption/use data for the ITs by drawing from the 2012 Kline report in the DRA. However, those data are now over a decade old and well out of date.[16] Most importantly, the marketplace for biocides has recognized the unique benefits IT chemistries can provide, and consequently, the use of ITs has grown significantly. In addition, the relatively good toxicological profile of ITs, which pose no chronic hazards, has become more important to industries that use biocides as regulatory pressures and public concern with chronic toxicity have adversely impacted the availability of other biocidal alternatives.

A critical aspect of the benefits assessment must focus on the availability, risks and effectiveness of other chemistries that might be considered alternatives to ITs. The Task Force and downstream user industries will explain that ITs provide unique benefits. While other chemistries can provide efficacy, each has its own toxicology profile and would virtually have to be applied at much higher use rates to obtain equivalent efficacy. In addition, any conversion to alternatives will impose very substantial research, development and transition costs on industries that rely upon ITs to provide antimicrobial protection today.

For these reasons, the IT Task Force urges EPA to adopt the modifications to its risk assessment methodology set forth in these comments, along with voluntary use rate reductions undertaken by registrants, which generate acceptable risks under most use scenarios EPA considers in its DRA. Where risks remain, the Task Force urges EPA to acknowledge the substantial benefits of ITs and not require any mitigation beyond the use rate reductions explained below.

[16] Specialty Biocides: Regional Market Analysis 2012-United States (April 3, 2013).

Further, as detailed in these comments, EPA made several mistakes when calculating risks. It also did not incorporate the best science into the human health and ecological risk assessments. Thus, the Task Force requests that EPA reissue the DCOIT DRA, incorporating all of the corrections, changes, and information presented in these comments. EPA should not proceed with issuing a Proposed Interim Decision or any risk mitigation for DCOIT until the record is corrected and stakeholders are provided another opportunity to comment.

II. HUMAN HEALTH RISK ASSESSMENT

The Task Force reviewed the EPA's DCOIT human health risk assessment. As discussed below, the Task Force finds that the EPA's assessment needs to be revised, and the corrections referred to in Section II.A of these comments were applied to the risk calculations presented in Sections II.B and II.C of these comments.[17]

There is potential for residential handler and residential post application exposure when using paints that are preserved with DCOIT. However, the Task Force finds that –

- EPA's assumption regarding the quantity of paint that a residential do-it-yourself (DIY) painter applies is not realistic; and
- EPA's assumption that 100% of the DCOIT used to treat an article is transferred to the skin is not realistic and does not consider the Standard Operating Procedure (SOP) for Residential Exposure and Risk Assessment for Pesticides (2012).

There is potential for exposure to DCOIT when handling DCOIT to preserve materials (such as paints) in the manufacturing process, and when using treated articles that are preserved with DCOIT (such as paints). However, the Task Force finds that –

- EPA incorrectly used the total conventional liquid pour dermal and inhalation unit exposures from the Antimicrobial Exposure Assessment Task Force II (AEATF II) liquid pour study (MRID 48917401) to assess the addition of liquid preservatives to a paint manufacturing process; and
- EPA did not consider the use of a head coverings by professional painters in its assessment of risks from the use of airless sprayers.

A. EXPOSURE SCENARIOS

Section 3.9 Residential (Non-Dietary) Handler Exposure/Risk Characterization

The assumption that a residential do-it-yourself (DIY) painter applies three 5-gallon cans (15 gallons) of paint in a day using an airless sprayer is not supported by a recent survey completed by the American Coatings Association (ACA) of paint manufacturers (Paint Industry Survey).[18] According to the ACA's data, less than 10 gallons of paint is used by the average consumer in a day, not the 15 gallons used in the EPA's airless spraying assessment. *A more realistic, yet*

[17] The following analysis was based on a report prepared for the Task Force by Leah Rosenheck, President, LR Risk Consulting, Inc.

[18] *See also* comments from the American Coatings Association, Docket IDs: EPA-HQ-OPP-2014-0160, EPA-HQ-OPP-2014-0159, EPA-HQ-OPP-2015-0736, EPA-HQ-OPP-2013-0605, and EPA-HQ-OPP-2014-0403.

conservative, default of 10 gallons of paint should be used to assess risks to consumer painters using airless spray.

Section 3.10 Residential Post Application Exposure

The Agency incorrectly assumed that 100% of DCOIT transfers from the treated article to the skin in its residential dermal post-application risk assessment.[19] As noted in the DRA, the AEATF II designed and is conducting residue removal/transfer studies. These studies are designed to refine the 100% default assumption used in the DRA. Although the AEATF II studies are not yet available, it is inappropriate for EPA to assume 100% transfer of biocide from the treated article.

Using the Residential SOP (2012), for contact with hard surfaces and flooring, the transfer efficiency is 0.08 (equivalent to 8%), and when in contact with treated textiles or carpeting, the transfer efficiency is 0.06 (equivalent to 6%). These transfer efficiency factors are sufficiently conservative, and it is unlikely that the transferable residue from DCOIT treated materials will be underestimated.

Further, use and usage information from the Task Force members revealed details about the industrial treatment process, which shows that for some active ingredients and treated articles, there is no potential for post application exposure.[20]

The Task Force provides recalculated MOEs using the transfer efficiencies from EPA's Residential SOPs.

Section 3.13 Occupational Handler Exposure/Risk Characterization

1. *Materials Preservation Handlers – Use and Usage Information*

The previously referenced ACA Paint Industry Survey includes information on the potential exposure to ITs during the paint manufacturing process. Although the respondents were only from the paint industry, similar practices would be observed by other manufacturing industries when applying ITs as materials preservatives.

The ACA survey respondents indicated that medium or large-scale production facilities use automated transfer systems to add the preservatives components into the product formulations. On the other hand, small-scale facilities are more likely to manually add biocides into the system. When considering small scale facility operations, EPA incorrectly assumed that only one employee adds the preservative biocides to the product produced during a work shift. In fact, there are multiple employees working in different departments on several different tanks at a time, and thus, the handling of biocide preservatives is borne by several employees and not one.

The results of the Paint Industry Survey confirm the use of PPE. Respondents indicated that PPE typically includes face shields, aprons, respirators (full and half mask), safety glasses or goggles,

[19] *See* DCOIT DRA Table 13.

[20] *See* Appendix B of these comments.

and long plastic gloves or latex gloves in addition to standard protective uniform clothing and shoes. Some facilities reported that their workers wear Tyvek suits and respirators with P100 filters (designed to filter out 99.97% of airborne particles) while handling biocides.

2. Information on Materials Preservation Formulations, Container Sizes, and Packaging

The Task Force wants to clarify that registered Technical Grade Ingredients (TGI/MUP) are not sold to manufacturing facilities that make paint, adhesives, and other types of treated articles. TGI/MUPs are used in highly controlled production plants to produce the end-use material preservatives or plastic pellets that are then sold to downstream industrial manufacturing customers. It is the end-use products that are the registered materials preservatives that are purchased and used by companies such as paint manufacturing facilities. This is an important distinction.

Information on packaging and container sizes was collected to better understand the division between containers that are manually poured versus those that require a mechanical (closed) transfer system.[21] Based on feedback from the Task Force, there are a variety of container sizes sold for liquid formulations, ranging in size from small jugs (1, 2.5, or 5-gallon capacity) to bulk containers (>500-gallon capacity). Most liquid preservatives are packaged in 15, 30 or 55-gallon drums or 250 to 500-gallon totes. This aligns with the input from the paint manufacturers, the majority of whom use a closed-transfer system to add liquid preservatives from drums and totes to the paint manufacturing process.

The plastic pellet and fused solid formulations are categorized as low exposure formulations and are not assessed in the pour solid handler risk assessments.

3. Pour Liquid Unit Exposures

The Task Force refined the dermal and inhalation unit exposures from the AEATF II liquid pour study (MRID 48917401) to assess the addition of liquid preservatives during the paint manufacturing process.[22] Rather than using entire dataset, the monitoring events from Group 1 (pouring from smaller containers) should be excluded. Group 1 contained three monitoring events (MEs 2, 4, and 6) that were done by pouring from 24, 32, and 64 oz bottles, which is not reflective of the larger jugs and open buckets that would be used to manually transfer liquid preservatives in an industrial setting.

The AEATF II liquid pour data provides a conservative estimate of exposure for paint/adhesives manufacturing because several of the monitoring events required test subjects to first pour into small measuring cups, which increased the potential for exposure and is not reflective of use patterns in large scale industrial operations such as paint manufacturing.

[21] *Id.*

[22] *See* the DCOIT DRA, Table 19.

Removing the three MEs from Group 1 results in a dermal unit exposure (with gloves) of 0.476 mg/lb ai and an inhalation exposure of 0.0014 mg/lb ai (compared to the unit exposures of 0.92 mg/lb ai and 0.0017 mg/lb ai for dermal and inhalation, respectively).

In these comments, the Task Force provides recalculated MOEs using the revised dermal and inhalation unit exposures.

4. Paint Applications/Professional Painters

EPA did not consider the use of head coverings by professional painters in its assessment of risks from the use of airless sprayers.[23] The AEATF II airless spraying study (MRID 50879401) shows that a professional painter wears a head covering such as a ball cap, painters cap, bandana, or a painter's spray sock to keep paint off of the hair. In addition, most professional painters use N95 disposable filtering facepieces or half-face paint respirators when using an airless sprayer. This type of PPE is co-marketed with the paint itself, which has led to routine use.

Use of protective equipment, which EPA acknowledged is used by the painters, should be included in the calculations for the airless spraying risk assessments and is reflected in the Task Force's recalculations of the dermal MOEs in these comments.

B. INHALATION

Section 3.6 Toxicity Endpoint and Point of Departure Selections

Short-/Intermediate-/Long-term Inhalation:

The Agency used the DCOIT-specific 90-day inhalation toxicity study (MRID 43487501) to assess inhalation risk for DCOIT.

Task Force Response:

The Task Force does not concur with EPA's selection of the 90-Day inhalation study in rats with DCOIT and the use of the NOAEL of 0.02 mg/m3 (HEC = 0.0045 mg/m^3) for inhalation exposure risk assessment based on the following considerations. Instead, the Task Force proposes alternative endpoints and points of departure to assess the risk from inhalation route of exposure to DCOIT formulations. This information is presented below, and a full report substantiating our use of the alternative data and endpoints is provided in Appendix C.

In the two-generation reproduction study, offspring toxicity manifested through clinical signs, decreased pup weight, and decreased organ weight (spleen and/or thymus) and/or delays in vaginal opening and preputial separation secondary to reduced body weight. in the F1 pups. This endpoint was used for dietary (chronic) and non-dietary (incidental oral) risk assessments. When there is a concern for effects in the fetuses in a developmental toxicity study or in the offspring in a reproductive toxicity, OPP's guidance is to use these effects as the endpoint of concern for

[23] *Id.*

inhalation risk assessment since the route-specific inhalation study does not evaluate the potential for developmental and reproduction endpoints (USEPA, 1998).

In the DCOIT inhalation study, treatment-related findings were primarily limited to the portal-of-entry effects in the nose, larynx, and lungs at the mid and high dose groups. There was a 31.5-fold difference between the low and the mid dose; therefore, the selected concentrations were not spaced appropriately to produce a concentration-response curve. The study authors did not provide criteria that was considered in identifying adverse, nonadverse, and adaptive findings. The decision about whether or not test article–related effects (or a group of related effects) in a non- clinical study are considered adverse or non- adverse should be unambiguously stated and justified in study reports. Consequently, there is potential for changes in the conclusion of the respiratory tract lesions observed if the current nomenclature, descriptors, and the criteria for grading the severity are utilized in the evaluation of the DCOIT inhalation toxicity study. Such an evaluation can make differences in interpretation and characterization of "adverse" vs. "non-adverse effects. In deciding whether an effect is adverse or adaptive, it is less likely to be considered adverse if the effects do not induce alterations in the tissues or organs, the effects are transient, or the effect is limited. Thus, there is low confidence in design, conduct and results of this study due to the poor dose selection and data analysis which could impact the decision-making process of arriving at NOAEC/LOAEC values.

More importantly, the developmental effects observed in the male and female offspring following oral exposure are adverse effects. They signify a more sensitive endpoints for risk assessment than the local irritation effects at the port of entry seen via inhalation exposure which are reversible upon cessation of exposure. Since the inhalation study is not designed to evaluate the potential for offspring toxicity there is residual uncertainty for this endpoint via the inhalation route. This uncertainty is addressed by the application of an additional 10x Modifying Factor. This POD will be protective of female workers and home makers of childbearing age and their infants as well as the male population since adversity in offspring can manifest through either sex. This POD will also be protective of the respiratory tract irritation seen in the inhalation study.

A route-specific study should be determined to be not appropriate for risk assessment when there are potential risks for a specific endpoint(s) identified in the oral studies which are not evaluated in the route-specific study. Under this condition, the appropriate oral study with the most sensitive endpoint will be used for risk assessment. Under this situation, when an oral NOAEL based on the sensitive endpoint is selected, typically the LOC is a target MOE of 100 which includes the conventional Uncertainty Factors (UFs) of 10x for inter-species extrapolation and 10x for intra-species extrapolation. However, in this situation, even though an oral NOAEL is proposed for inhalation risk assessment, a target MOE of 1000 is proposed.

The oral study chosen identified significant developmental effects (decreased pup body weight and decreased spleen and/or thymus weight and delayed sexual maturation secondary to reduced pup weight) in the offspring (the most sensitive endpoint) via the oral route. In contrast, an inhalation study identified only portal-of-entry effects, related to the irritant properties of the chemical which are reversible. Thus, uncertainty is increased for the potential reproductive toxicity via the inhalation route. This uncertainty is addressed by the target MOE of 1000 which includes the conventional 100 and a 10x Modifying Factor.

The EPA's RfD Technical Panel states that in addition to the standard uncertainty factors, an additional modifying factor (MF) may also be applied when scientific there are uncertainties in the study chosen or database that are not explicitly addressed by the standard UFs. It is further stated that use of the factor depends principally on professional judgment and assessment (USEPA, 2002a). EPA's IRIS has used variable MFs for establishing RfD for chromium III, chromium VI, nitrite, and a RfC for acetonitrile (USEPA, 2002b).

Table 1. Revised Points of Departure Proposed for Inhalation Risk Assessment

Exposure Scenario	Points of Departure	Level of Concern	Study/Toxicological Effects
All Durations (short-, Intermediate-, and Long-Term	**Oral NOAEL= 30 mg/kg/day**	Occupational and Residential **Target MOE = 1000** $UF_A = 10$ $UF_H = 10$ MF =10 FQPA SF= 1X	Two-Generation Reproduction-Rat (MRID 4575656501) LOAEL=62 mg/kg/day based on based on decreased absolute and relative spleen and thymus weight and significantly delayed vaginal opening and preputial separation secondary to reduced body weight in F1 offspring.

Section 3.9 Residential (Non-Dietary) Handler Exposure/Risk Characterization

Section 3.9.1 Residential Handler Inhalation Exposure to DCOIT

EPA presented the Residential Handler Inhalation MOEs for DCOIT in Preserved Paint in DRA, Table 11. The MOE of 0.1 for airless spray is of concern because it is less than the LOC of 10.

Task Force Response:

The revised residential handler inhalation MOEs using an oral POD and the correct value of 10 gallons of paint applied per day by airless sprayer is presented in Table 2 below.[24] *There are no risks of concern since the MOEs are greater than the LOC for the short and intermediate duration of concern.*

Table 2. Revised EPA Table 11: Residential Handler Inhalation MOEs for DCOIT Preserved Paint

Paint Application Scenario	Application Rate[A]	Gallons of Paint Applied per Day	Amount a.i. Handled[C] (lb/day)	Unit Exposure (mg/lb a.i.)	Inhalation Exposure[F] (mg/kg/day)	MOE[G, H] LOC=1000
Airless Spray	2000 ppm a.i.	**10[B]**	0.20	0.993[D]	0.0024	12,500
Brush/Roller		2[B]	0.040	0.0078[E]	0.000004	7,500,000

[24] Refer to Section III.A. of these comments for background information.

A. The application rates are the maximum rates from the labels.
B. Revised default of 10 gallons of paint is used. (see Section II.A. of these comments)
C. Amount of a.i. Handled (lb/day) = Application Rate (ppm/1,000,000) x Amount Product Applied (gal) x Product Density (10 lb/gal)
D. AEATF II airless sprayer study (MRID 50879401).
E. AEATF II brush/roller study (MRID 50521701).
F. Inhalation Exposure (mg/kg/day) = Amount a.i. Handled (lb/day) x Unit Exposure (mg/lb a.i.) x 100% absorption /bw (80 kg)
G. MOE = Inhalation NOAEL (mg/kg/day) / Inhalation Exposure (mg/kg/day).
H. Inhalation NOAEL: oral POD 30 mg/kg/day, LOC=1000

3.13 Occupational Handler Exposure/Risk Characterization

Section 3.13.1 <u>Occupational Handler Inhalation Exposures to DCOIT:</u>

EPA presented the Occupational Handler Inhalation MOEs for DCOIT in DRA Table 18. The MOEs for open pour liquids for paint preservation and airless spray application of paint are both of concern because they are less than the LOC of 10.

<u>Task Force Response:</u>

The revised occupational handler inhalation MOEs using an oral POD and the corrected inhalation unit exposure for open pour liquids discussed in Section II.A. of these comments is presented in Table 3 below. There are no risks of concern since the MOEs are greater than the LOC of 1000 for short-, intermediate-, and long-term exposure durations.

Table 3. Revised EPA Table 18: Occupational Handler Inhalation MOEs for DCOIT

Scenario	Application Rate[A]	Amount of Product Applied or Material Treated per Day[B]	Amount a.i. Handled (lb/day)[C]	Inhalation Unit Exposure (mg/lb a.i.)	Inhalation[G] Exposure (mg/kg/day)	MOE[H,I] LOC=1000
Open pour liquids for paint preservation	2,000 ppm a.i.	20,000 lbs of paint	40	**0.0014[D]**	0.0007	42,000
Airless Spray Application of Paint	2,000 ppm a.i.	500 lb of paint	1.0	0.993[E]	0.0124	2,400
Brush/Roller Paint		50 lb of paint	0.10	0.0078[F]	0.000001	3,000,000

A. The application rates are the maximum rates from the labels.
B. Standard assumptions used for occupational exposure assessments of AD chemicals.
C. Amount of a.i. Handled (lb/day) = Application Rate (ppm/1,000,000) x Amount Product Applied or Treated (lbs).
D. **Unit exposure from AEATF II liquid pour study (MRID 48917401). Groups 2 and 3 only. (see Section II.A. of these comments)**
E. AEATF II airless sprayer study (MRID 50879401).
F. AEATF II brush/roller study (MRID 50521701).
G. Inhalation Exposure (mg/kg/day) = Amount a.i. Handled (lb/day) x Unit Exposure (mg/kg/day) x 100 absorption/ bw (kg).
H. MOE = Inhalation NOAEL (mg/kg/day) / Inhalation Exposure (mg/kg/day).

I. **Inhalation NOAEL: oral POD 30 mg/kg/day (All durations).**

Section 3.13.3 Shipyard Painter Exposures for DCOIT in Antifoulant Paints:

EPA presented the Shipyard Painters Inhalation MOEs in DRA Table 24. There is a risk of concern for Trial B spray men with an MOE of 1.9. There are no risks of concern for other job functions since the MOEs range from 22 to 280.

Task Force Response:

The Task Force revised shipyard painter MOEs using the oral POD without a respirator in Table 4 below. *There are no risks of concern for this scenario, except for the Trial B Spray Man, because the MOE of 132 is less than the LOC of 1000. This risk is mitigated with a PF10 respirator. With the respirator, the MOE is 1,320, which is not of concern because it is greater than the LOC of 1000.*

Although the risk of concern for the Trial B Spray man is addressed with a PF10 respirator, the Task Force does not believe that Trial B is representative of real-world exposure to antifoulant paints for professional painters. In the Trial B scenario, a plastic tent was positioned around the applicator, reducing air changes and drift, and thus effectively increasing the air concentration of the paint. The Task Force is unaware of any circumstance where tenting would be set up around an applicator, and this scenario should not be included in the evaluation of inhalation risks from application of marine antifoulant paints. If Trial B is excluded, there are no inhalation risks of concern for shipyard painters.

Table 4. Revised Table 24: Shipyard Painters Inhalation MOEs

Trial[A]	Job	Amount ZPT Handled During Study[B] (lb a.i./day)	Amount DCOIT Handled[C] (lb a.i./day)	Inhalation Unit Exposure[D] (µg/m³/lb a.i.)	Inhalation Exposure[E]		MOE[F] (LOC = 1000)
					(mg/m³)	(mg/kg/day)	
ACD	Spray Man	18.3	25.2	8.27	0.208	0.0241	**1,244**
	Line Tender	14.8	20.4	3.12	0.064	0.0074	**4,054**
	Pot Man	26.6	36.6	0.44	0.016	0.0019	**15,789**
B	Spray Man	11.8	16.2	149	2.41	0.2799	107
	Spray Man	11.8	16.2	149	2.41	0.2799	**1,071[g]**
	Line Tender	11.8	16.2	12.7	0.206	0.0239	**1,255**
	Pot Man	23.5	32.3	1.57	0.051	0.0059	**5,084**

A. Plastic tenting with a small exhaust fan was used during Trial B to prevent overspray.
B. Average values for each job. Amounts handled for multiple cycles per day were added together.
C. Amount DCOIT handled = Amount a.i. handled during study *(5.23 % DCOIT / 3.8% ZPT in study paint)
D. Are the Estimated Arithmetic Average (AMm) inhalation unit exposure values taken from Table 23 of the EPA risk assessment.
E. Inhalation Exposure (mg/m³) = Amount DCOIT Handled (lb a.i./day) * Inhalation Unit Exposure (µg/m³/lb a.i.) * 0.001 mg/µg
F. Inhalation Exposure converted to an adult daily dose (mg/kg/day) [(mg/m³) x (0.001 m³/L) x A x CF (L/h/kg) x D (hours)]
G. PF10 Inhalation MOE = Inhalation MOE / Protection Factor for respirator (10)
Inhalation NOAEL: oral POD 30 mg/kg/day (All durations).

Section 3.13.4 Pressure Treatment Worker Exposures to DCOIT:

EPA presented the Pressure Treatment Worker Inhalation MOEs in DRA Table 26. There are no risks of concern for this scenario.

Task Force Response:

While the EPA did not identify any risks of concern for this scenario, the Task Force recalculated the MOEs using the oral POD. The appropriate MOEs for pressure treatment worker using an oral POD are presented in Table 5 below. *There are no risks of concern for treatment operator or wood handler since the MOEs are greater than the LOC of 1000.*

Table 5. Revised EPA Table 26: Pressure Treatment Worker Inhalation MOEs

Job Function	Application Rate[A] (% a.i.)	Fraction a.i.[B]	Inhalation Unit Exposure[C] (µg/m³/fraction a.i.)	Inhalation Exposure[D]		MOE[E] (LOC = 1000)
				(mg/m³)[E]	(mg/kg/day)	
Treatment Operator	0.69	0.0069	3.0	0.000021	0.0000024	12,500,000
Wood Handler			11.6	0.00024	0.0000017	17,600,000

A. Application rate is for utility poles, cross arms and bridge timber listed on EPA Reg No. 83997-13.
B. Fraction a.i. = Application Rate (% a.i.) / 100
C. Estimated Arithmetic Average (AMm) for the 8- hour TWA total inhalable fraction unit exposures from the AEATF II Pressure
D. Treatment Exposure Study (MRID 49434501) for Sites ABDE.
E. Inhalation Exposure (mg/m³) = Fraction a.i. * Inhalation Unit Exposure (mg/m³/fraction a.i.) * 0.001 mg/µg
F Inhalation Exposure converted to an adult daily dose (mg/kg/day) [(mg/m³) x (0.001 m³/L) x A x CF (L/h/kg) x D (hours)]
G .**Inhalation NOAEL= oral POD 30 mg/kg/day (all durations)**

C. DERMAL

Section 3.6 Toxicity Endpoint and Point of Departure Selections

Short-/Intermediate-/Long-term Dermal:

The Agency selected the POD "based on the dermal sensitization induction threshold of 5.8 µg/cm² determined from the average EC3 value of 0.023% based on the Shiseido artificial neural network (ANN) Model (ANN D_hC_KS, "model 4" in Hirota *et al*. 2015)" for assessment of short, intermediate, and long-term dermal exposures of DCOIT.

Task Force Response:

The Task Force does not agree with EPA's selection of the induction POD for DCOIT. While EPA has stated that non-animal testing strategies, including ANN, are more reliable than LLNA for determination of skin sensitization potency, the Task Force strongly disagrees for the following reasons:

- The Shiseido ANN Model and the inputs are not appropriate for this class of chemicals for derivation of an EC3 value based on the inconsistencies in potency ranking between the

Shiseido ANN Model-derived EC3 values and the potency ranking demonstrated by LLNA and human data values for the isothiazolones;

- The Shiseido ANN Model uses inputs that are not applicable to substances with low solubility (Kleinstreuer et al., 2018). Because of the difference in solubilities of the isothiazolones, any potency ranking between ITs may be inaccurate using this methodology;
- *In-vitro* assays have received OECD approval for hazard identification purposes; however, these data have not been validated to derive sensitization potency when used in combination with Integrated Approaches to Testing and Assessment (IATA) and Defined Approaches; and
- Any integrated approach needs to be benchmarked back to available human sensitization data, and this has not been done for the Shiseido ANN Model.

HRIPT data are available that, in a weight of evidence approach with available LLNA data, provide an appropriate human relevant no expected sensitization induction limit (NESIL) for the ITs. EPA should use the available NESILs for dermal risk assessment because relevant human data are the gold standard for purposes of risk assessment and determining safe exposure levels for a product. LLNA data for the ITs were developed by benchmarking back to the available human data, and the LLNA data are consistent with the available HRIPT data in terms of potency ranking across members of the IT class of chemistries.[25] In addition, use of human data avoids complications and uncertainty of the need to extrapolate from mouse to humans when LLNA data are used.

Based on the foregoing, the induction threshold for DCOIT is 6.3 $\mu g/cm^2$. Because the weight of evidence NESIL considers available human data, the uncertainty factor (UF) for interspecies variation is not needed and the Level of Concern (LOC) is the target MOE of 10 based only on potential intraspecies variation.

We elaborate on these points below.

1. Inappropriate Use of ANN Model and *In Vitro* Data for Quantification of Skin Sensitization

The Task Force reviewed the U.S. EPA Hazard Characterization of Isothiazolinones in Support of FIFRA Registration Review (Hazard Characterization Report), which was prepared in collaboration with the National Toxicology Program's Interagency Coordinating Committee for the Evaluation of Alternative Toxicological Methods (NICEATM) and provides the hazard characterization assessment for the IT risk assessment.[26] A full critique of the Hazard Characterization Report, authored by Drs. Ian Kimber and Frank Gerberick, is provided in Appendix C of these comments. Key points from the Kimber/Gerberick report discussed below.

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[25] MRID 51201501 Ladics, G. (2020) Skin Sensitization Potency Comparison (Kathon 886F Industrial Microbiocide). Project Number: NB/200040/1730. Unpublished study prepared by GF3 Consultancy, LLC. 27p.

[26] Office of Chemical Safety and Pollution Prevention, U.S. Envtl. Prot. Agency, Hazard Characterization of Isothiazolinones in Support of FIFRA Registration Review (April 6, 2020).

Among the 6 methods considered by Kleinstreuer et al. (2018) was the Artificial Neural Network (ANN) model.[27] This method seeks to predict LLNA EC3 values using various combinations of three types of *in vitro* tests: (1) SH protein reactivity test or Direct Peptide Reactivity Assay [DPRA], (2) human Cell Line Activation Test [h-CLAT], and (3) an antioxidant response element [ARE] test or KeratinoSens. The Hazard Characterization Report states that of the 6 approaches evaluated by Kleinstreuer et al (2018) '*the artificial neural network (ANN) model …*was *...unique in its ability to estimate LLNA EC3 values*.[28] The data generated with the ITs, however, do not support this view.

EC3 values generated using ANN models were compared with those derived from LLNA studies (Table 6). This is, of course, relevant because the stated aim of the ANN approach was to develop a system to replace the LLNA (Hirota et al., 2015).

Table 6: EC3 Values (%) Measured in the LLNA and Estimated from Three ANN Models

Chemical	LLNA	ANN Models[A]		
		h-CLAT+DPRA	h-CLAT+DPRA+ARE	h-CLAT+SH+ARE
CMIT/MIT	0.005	0.13	0.10	0.07
MIT	1.9	0.70	-	-
BIT	2.3	0.03	-	-
A. Hirota et al (2015)				

It is clear from the data in Table 6 that there are significant differences between LLNA EC3 values and EC3 values estimated from the ANN models. The EC3 value for CMIT/MIT is substantially higher than the LLNA EC3 value by a factor of 26 in the h-CLAT+DPRA model, by a factor of 20 in the h-CLAT+DPRA+ARE model, and by a factor of 14 in the h-CLAT+SH+ARE model. In contrast, the predicted EC3 values for MIT and BIT in the h-CLAT+DPRA model are lower, and in the case of BIT substantially lower, than the relative LLNA EC3 values. The EC3 value for MIT in the h-CLAT+DPRA model was lower by a factor of 2.7 than the LLNA EC3 value, and the EC3 value for BIT in the h-CLAT+DPRA model was lower by a factor of 76.7 than the LLNA EC3 value.

Further, in the Hazard Characterization Report two ANN models were evaluated: (1) h-CLAT+DPRA and (2) h-CLAT+DPRA+ARE (in this case the ARE used was KeratinoSens).[29] These data, along with LLNA data, are summarized below in Table 7 where all EC3 values are recorded as % values.

Table 7: EC3 Values (%) Measured in Two Separate LLNA Assessments, and EC3 values (%) and Predicted by Two ANN Models

IT	LLNA (1) (Dow)	LLNA (2) (EPA)	ANN Models[A]	
			h-CLAT+DPRA	h-CLAT+DPRA+ARE
DCOIT	0.004	0.004	0.0566	0.023

[27] *Id.* at 13.

[28] *Id.* at 13.

[29] *Id.* at 17.

CMIT/MIT	0.002	0.018	0.121	0.492
OIT	0.225[B]	0.361	0.0569	0.015
MIT	0.863	1.154	1.775	0.826
BIT	1.54	10.57	0.934	0.341
A. Hirota et al (2015) B. Average of 2 values (0.20 and 0.25)				

The data summarized in Table 7 are not dissimilar to those in Table 6. When considering both sets of data, it can be concluded in that:

- EC3 values measured in the LLNA were substantially lower than EC3 values predicted using ANN models for CMIT/MIT.
- EC3 values measured in the LLNA were 2-3-fold higher or lower than EC3 values predicted using ANN models for MIT.
- EC3 values measured in the LLNA were substantially higher than EC3 values predicted using ANN models for BIT
- EC3 values measured in the LLNA were lower/substantially lower than EC3 values predicted using ANN models for DCOIT.
- EC3 values measured in the LLNA were higher or substantially higher than EC3 values predicted using ANN models for OIT.

Compared with EC3 measurements made using the LLNA, the ANN models under-predict the potency of CMIT/MIT and DCOIT and over-predict the potency of BIT and OIT. Although there are differences, the EC3 values for MIT from the LLNA and ANN models are broadly comparable. Despite the marked differences between the EC3 measurements using the LLNA and the ANN models, the EPA/NICEATM report concludes that "the quantitative EC3 predictions derived from the ANN Das were similar to the LLNA EC3 values, with overlapping 95% confidence intervals in most cases, with the exception of CMIT/MIT."[30] The confidence intervals were substantial, and this supports the fact that the *in vitro* data has a great deal of variability and is not appropriate for use in the risk assessment.

The differences between the LLNA EC3 values and the ANN predicted EC3 values also result in an inaccurate rank order of potency among the ITs. The Task Force believes these differences are attributable to the fact that ITs are not applicable to the ANN models.

EPA's Hazard Characterization Report acknowledges that none of the validated non-animal methods that has been assigned OECD test guideline status are currently accepted as stand-alone methods for the purposes of hazard identification.[31] While *in-vitro* assays have received OECD approval for determining whether a product is a skin sensitizer or not (*i.e.,* for hazard identification purposes), these data have not been validated to derive sensitization potency when used in combination with IATA and Defined Approaches. Further, benchmarking to available LLNA and human data demonstrates these non-animal strategies do not accurately inform the potency of ITs. Because the use of the *in vitro* assays has not been validated for the purposes of measuring skin

[30] *Id.* at 16.

[31] *Id.* at 11 – 12.

sensitizing potency, and they do not accurately inform the potency for this class of chemicals, this data should not be used in the risk assessment.

In addition, it is worth noting that – in common with other *in vitro* methods – chemicals that are poorly water soluble likely are not applicable with the ANN models. There is also no available data on the vehicles that were used for assessment of the ITs using the ANN models. At this time, ANN models cannot be considered to provide an accurate indication of skin sensitizing potency, and it would be inappropriate to use EC3 values predicted by ANN models in the assessment of skin sensitization risks posed by exposure to ITs.

2. Integrated Approach Using Human Studies and LLNA

Any approach to address dermal sensitization should utilize an integrated approach where human studies play a predominant role. As previously noted, EPA's current approach using the Shiseido ANN Model is not appropriate for several reasons, one of which is the fact that this data has not been benchmarked against the available human data. LLNA data on the other hand, has been benchmarked again human data, and the results of the LLNA data align with that of the human data. A more appropriate approach to assess the dermal sensitization of ITs is a Weight of Evidence (WOE) approach using the human studies and LLNA data.

Approximately 23 human dermal sensitization studies on the ITs, including OIT, were submitted to EPA and are critical to consider in the evaluation of dermal risks to the ITs.[32]

While the Task Force recognizes that EPA is prohibited from considering the human studies until the Human Studies Review Board (HSRB) conducts a review, we provide the following evaluations from Drs. Ian Kimber and Frank Gerberick, known experts in the field of dermal sensitization, who reviewed the conduct, interpretation, and ethics of all the human studies.[33] Drs. Kimber and Gerberick concluded that the human dermal sensitization studies provided "are very valuable for developing accurate assessments of skin sensitization risks for the 5 isothiazolinones considered." The authors did not find any concerns about ethical standards, and there were no indications that studies had been unnecessarily duplicated.

The available human studies and LLNA data were considered by Dr. Gerberick in a WOE approach to determine NESIL values.[34] Subsequently, for DCOIT, additional LLNA data were also considered (MRID 51385201). Combining the LLNA data with the studies considered by Dr. Gerberick in a WOE approach results in the NESIL values presented below in Table 8.

Table 8. Isothiazolinone Potency Ranking by WoE NESIL

IT	LLNA EC3 Range µg/cm²	LLNA EC3 Median[A] µg/cm²	Human NOEL µg/cm²	Human LOEL µg/cm²	WoE NESIL µg/cm²

[32] These studies are awaiting review by the Human Studies Review Board (HSRB).

[33] MRID 51383906.

[34] MRID 51201501.

CMIT/MIT	0.65 – 52.5	1.9	0.8	~ 2	0.8
DCOIT	1.02 – 15.0[B]	6.3[C]	NA[D]	12.5	6.3[E]
OIT	50 – 165.6	72.6	2.7	5.6	2.7
MIT	216 – 550	345.5	15	20	15
BIT	385 – 8100	575	55.6	90.6	55.6

A. Number of LLNA studies used to calculate mean: CMIT/MIT, N=10); DCOIT, N=2; OIT, N=4; MIT, N=4; and BIT, N=7.
B. Include Dupont data summarized by Dr. Gerberick (MRID 51201501), as well as additional LLNA data (MRID ?).
C. Values reported are the mean
D. Data not available
E. This value differs from the summary from Dr. Gerberick (MRID 51201501) because it incorporates additional LLNA data (MRID 51385201). The NESIL is the mean of the available DCOIT data.

Based on the results in Table 8, the mean EC3 value of 6.3 µg/cm^2 is considered as the refined NESIL. The Task Force believes the WoE NESIL value to be the best available science to assess skin sensitization risks associated with exposure to DCOIT. This NESIL value is approximately half of the human LOEC provided by available HRIPT data, demonstrating good correlation between the animal and human data. Based on the human and animal data being highly correlated, and considering that the human LOEC of 12.5 µg/cm^2 is anticipated to be at or near the threshold for sensitization in humans based on available data, an interspecies uncertainty factor is not applied and the LOC is equal to the intraspecies uncertainty factor of 10.

Section 3.9 Residential (Non-Dietary) Handler Exposure/Risk Characterization

Section 3.9.2 Residential Handler Dermal Exposure to DCOIT:

EPA presented the Residential Handler Dermal MOEs for DCOIT in DRA Table 12. The MOEs for airless spray (MOE = 0.6) and brush/roller (MOE = 1.1) are both of concern because they are less than the LOC of 100.

Task Force Response:

Residential handler dermal MOEs for DCOIT based on the Task Force's revised POD and the corrected amount of product applied of 10 gallons per day for airless spray application of paint discussed in Section II.A. of these comments are presented in Table 9 below. *The MOEs are still both of concern because they are less than the LOC of 10.*

Table 9. Revised EPA Table 12: Residential Handler Dermal MOEs for DCOIT Preserved Paint

Paint Application Scenario	Application Rate[A]	Gallons of Paint Applied per Day	Amount a.i. Handled[D] (lb/day)	Dermal UnitExposure (mg/lb a.i.)	Dermal Exposure[G] (mg/day)	Dermal Loading[H] (µg/cm2)	MOE[I] LOC = 10
Airless Spray	2000 ppm a.i.	**10[B]**	0.20	105[E]	21.0	6.4	**1.0**
Brush/Roller		2[C]	0.04	144[F]	5.8	5.3	**1.2**

A. The application rates are the maximum rate from the labels.
B. Revised maximum amount handled per day. (see Section II.A. of these comments)
C. Based on US EPA, 2012a.
D. Amount of a.i. Handled (lb/day) = Application Rate (ppm/1000000) x Amount Product Applied (gal) * Product Density (lb/gal)
E. Short sleeve short pants value from the AEATF II airless sprayer study (MRID 50879401). Hand Exposure = 25%.
F. Short sleeve short pants value from the AEATF II brush/roller study (MRID 50521701). Hand exposure = 76%.
G. Dermal Exposure (mg/day) = Amount a.i. Handled (lb/day) * Unit Exposure (mg/lb a.i.)
H. Dermal Loading = [Dermal Exposure (mg/day) * Hand Exposure (%/100) * 1000 µg/mg]/Hand Area (820 cm^2)
I. MOE = POD (6.3 µg/cm^2) / Dermal Loading (µg/cm^2)

Section 3.10 Residential Post-Application Exposure

Section 3.10.1 Residential Post Application Exposures from DCOIT in PVC Flooring:

EPA presented the Post Application Dermal MOEs for DCOIT in PVC Flooring in DRA Table 13. The MOE of 1.5 is of concern because it is less than the LOC of 100.

Task Force Response:

The post application dermal MOE for DCOIT in PVC flooring based on the Task Force's revised POD and applying the transfer factor from the EPA Residential SOPs (2012) as discussed in Section II.A. of these comments is presented in Table 10 below. *There is no risk of concern for DCOIT in PVC flooring because the MOE is greater than the LOC of 10.*

Table 10. Revised EPA Table 13: Dermal MOE for DCOIT in PVC Flooring

Application Rate[A] (ppm)	Flooring Density[B] (mg/cm^2)	Floor Thickness (cm)	Availability Factor (%)	Surface Residue[C] (mg/cm^2)	Transfer Factor[D] (Fraction)	Dermal Loading[E] (µg/cm^2)	Dermal MOE[F] (LOC = 10)
2000	1,300	**0.3**	**0.5**	0.0039	**0.08**	0.312	**20.2**

A. Based application rate for PVC floor coverings
B. From EPA Residential SOPs (2012), Impregnated Materials, Table 9-2, vinyl flooring.
C. Surface Residue (mg/cm^2) = Application rate/1,000,000 x Density (mg/cm^2)
D. From EPA Residential SOPs (2012), Impregnated Materials, Table 9-2, flooring transfer efficiency (see Section II.A. of these comments)
E. Dermal Loading (µg/cm^2) = Surface Residue (mg/cm^2) x Transfer Factor x (1000 µg/1 mg)
F. **Dermal MOE = 6.3 µg/cm^2 / Dermal Loading µg/cm^2, LOC = 10**

Section 3.10.2 Residential Post Application Exposures from DCOIT Treated Wood:

EPA presented the Children's Dermal MOEs when Contacting DCOIT-treated Decks/Playsets in DRA Table 16. The MOEs are all less than the LOC of 100 and thus are of concern.

Task Force Response:

EPA based their assessment of children's dermal MOEs when contacting DCOIT-treated decks/playsets on two products: 1) EL2 One-Pack and 2) Viance 11-2016. EPA notes that the assessment of Viance 11-2016 was because it is similar to 707-307. This is not true. Viance 11-2016 is for treatment of industrial wood, such as utility poles and railroad ties, and 707-307 is for

treatment of lumber such as decking, fencing, millwork and joinery. As such, the assessment of Viance 11-2016 should be removed from the DRA.

Revised MOEs for children's contact of DCOIT treated decks/playsets based on the Task Force's revised POD are presented in Table 11 below. *The MOEs are greater than the LOC of 10, and therefore not of concern.*

Table 11. Revised EPA Table 16: Children's Dermal MOEs When Contacting DCOIT Treated Decks/Playsets

Treatment Solution DCOIT Content	Target Retention (pcf)	Measured Retention (pcf)	Dislodgeable Residue (µg/cm^2)	Dermal MOE[A] (LOC = 10)
0.13%	0.04	0.042 to 0.048	0.21 0.11	**30** **57**
A. Dermal MOE = 6.3 µg/cm2 / dislodgeable residue (µg/cm2), LOC = 10				

3.13 Occupational Handler Exposure/Risk Characterization

Section 3.13.2 Occupational Handler Dermal Exposures:

EPA presented the Occupational Handler Dermal Exposure MOEs for DCOIT in DRA Table 19. The MOEs are all less than the LOC of 100 and thus of concern.

Task Force Response:

Occupational handler dermal exposure MOEs for DCOIT based on the Task Force's revised POD are presented in Table 12 below. Based on Section II.A. of these comments, for open pour liquids, the assessment employed the corrected value of 0.476 mg/lb ai, and for airless spray application of paint, the assessment accounts for head coverings worn by painters. *The MOEs are below the LOC of 10 and therefore still of concern.*

Table 12. Revised EPA Table 19: Occupational Handler Dermal MOEs for DCOIT

Scenario	Application Rate[A]	Amount of Product Applied or Material Treated per Day[B]	Amount a.i. Handled[C] (lb/day)	Dermal UnitExposure (mg/lb a.i.)	Dermal Exposure[G] (mg/day)	Dermal Loading[H] (µg/cm^2)	Dermal MOE[I] LOC = 10
Open pour liquids for paint preservation	2,000 ppm a.i.	20,000 lbs of paint	40	**0.476[D]**	19.0	22.9	**0.27**
Airless Spray Application of Paint	2,000 ppm a.i.	500 lb of paint	1.0	**31.8[E]**	31.8	23.3	**0.27**

Brush/Roller Paint Application		50 lb of paint	0.10	115[F]	11.5	13.2	**0.5**

A. The application rates are the maximum rates from the labels.
B. Standard assumptions used for occupational exposure assessments of AD chemicals.
C. Amount of a.i. Handled (lb/day) = Application Rate x Amount Product Applied or Treated.
D. Conventional pour value from groups 2 and 3 of the AEATF II human exposure liquid pour study (MRID 48917401) divided by 10X to account for the use of gloves. Hands = 99%. (see Section II.A. of these comments)
E. Long sleeve long pants head covering value from the AEATF II Airless Sprayer study (MRID 50879401). Hand exposure = 60%. (see Section II.A. of these comments)
F. Long sleeve long pants, no gloves value from the AEATF II brush/roller study (MRID 50521701). Hand exposure = 94%.
G. Dermal Exposure (mg/day) = Amount a.i. Handled (lb/day) * Unit Exposure (mg/m3/lb a.i.)
H. Dermal Loading = [Dermal Exposure (mg/day) * Hand Exposure (%/100) * 1,000 µg/mg] / Hand Area (820 cm^2)
I. MOE = POD (6.3 µg/cm^2) / Dermal Loading (µg/cm^2)

Section 3.13.3 Shipyard Painter Exposures to DCOIT in Antifoulant Paints:

EPA presented the Shipyard Painter Worker Dermal Exposure MOEs for DCOIT in Table 25. The MOEs based on the chest patches range from 0.04 to 5.4 and are all of concern because they are less than the LOC of 100. The MOEs based on the inner glove dosimeters range from 0.2 to 130 and all but one are of concern.

Task Force Response:

Occupational handler dermal exposure MOEs for DCOIT based on the Task Force's revised POD are presented in Table 13 below. The chest patches considered by EPA are not included by the Task Force because these are not reflective of actual exposure conditions. Shipyard workers wear full Tyvek suits, including hood or head covering and full face respirator. As such, there should be no uncovered skin on the face or neck that can be exposed to antifouling paint during application. We also note that in the ZPT study, different gloves were used in Trial A versus Trial B, C, and D. The work gloves used in Trial A are not representative of appropriate or recommended PPE for application of antifouling paint and are not expected to provide sufficient protection from dermal exposure. Trials B, C, and D, performed with chemical-resistant gloves, are more representative of recommended PPE. We suggest that further refinement of dermal loading values, considering this point, is needed. However, without this additional refinement, the MOEs are below the LOC of 10 for most trial/job combinations and therefore still of concern.

Table 13. Revised EPA Table 25: Shipyard Painter Dermal MOEs for DCOIT

Trial[A]	Job	Amount ZPT Handled During Study[B] (lb a.i./day)	Amount DCOIT Handled[C] (lb a.i./day)	Measured Dermal Loading[D] (µg/cm^2)	Adjusted Dermal Loading[F] (µg/cm^2)	Dermal MOE[F] LOC = 10
ACD	Spray Man	18.3	25.2	17.7	24.4	**0.26**
	Line Tender	14.8	20.4	19.6	26.9	**0.23**
	Pot Man	26.6	36.6	14.1	19.4	**0.32**
B	Spray Man	11.8	16.2	1.6	2.2	2.9
	Line Tender	11.8	16.2	0.57	0.78	8.1
	Pot Man	23.5	32.3	0.032	0.044	143

A. Plastic tenting with a small exhaust fan was used during Trial B to prevent overspray.
B. Average values for each job. Amounts handled for multiple cycles per day were added together.
C. Amount DCOIT handled = Amount a.i. handled during study *(5.23% DCOIT / 3.8% ZPT in study paint)
D. Arithmetic average amount on the inner glove dosimeters divided by the hand area of 820 cm^2.
E. Adjusted Dermal Loading (µg/cm^2) = Amount DCOIT Handled (lb a.i./day) / Amount ZPT Handled during Study (lb a.i./day) * Measured Dermal Loading (µg/cm^2). Results are reported for hands only.
F. Dermal MOE = POD (6.3 µg/cm^2) / Adjusted Dermal Loading (µg/cm^2). Results are reported for hands only. LOC = 10.

D. CONCLUSIONS – HUMAN HEALTH RISK ASSESSMENT

1. Inhalation

Residential Exposure

There are no risks of concern via inhalation exposure for residential handlers when applying paints using an airless spray (MOE = 12,500) or brush/roller (MOE=7,500,000) because the MOEs are greater than the LOC of 1000.

Occupational Exposure

There are no risks of concern for inhalation exposure to occupational handlers during open pour liquids of paint preservatives (MOE=35,000) and when using an airless paint spray (MOE = 2,400) or brush/roller (MOE=3,000,000) because the MOEs are greater than the LOC of 1000.

There are no risks of concern for inhalation exposure to shipyard workers spraying antifoulant paint and to pressure treatment workers because the inhalation greater than the LOC of 1000.

2. Dermal

Residential Exposure

There are no risks of concern from post application dermal exposure to DCOIT in PVC flooring (MOE = 20.2) and for children when contacting treated decks/playsets (MOEs = 30 to 57) since the MOEs are greater than the LOC of 10.

There are risks of concern for residential dermal exposure to from DCOIT-preserved paint using an airless spay (MOE = 1) or brush/roller (MOE = 1.2) since the MOEs are less than the LOC of 10.

Occupational Exposure

There are risks of concern for dermal exposure to occupational handlers during open pouring of liquids for paint preservation (MOE = 0.27) and when applying paints using an airless spray (MOE = 0.27) or brush/roller (MOE = 0.5) since the MOEs are less than the LOC of 10. There are also risks of concern shipyard painters in Trials A, C, and D (MOEs = 0.26 – 0.32) and in Trial B for Spray Man (MOE = 2.9) because the MOEs are less than the LoC of 10.

III. CONCLUSIONS

The Agency's DCOIT DRA calculates high human health risks by combining unrealistic exposure assumptions with unrealistic calculated toxicity hazards. In its comments above, the Task Force has provided more realistic human exposure estimates and more accurate assessments of potential toxicity. Applying those values results in risk calculations that, for many uses, meet EPA's target as demonstrating no risk. For uses for which calculated risks continue to appear to be above EPA's levels of concern, the Task Force maintains no mitigation is necessary or appropriate in light of the unique and substantial benefits of IT biocides. In addition, the absence of reported issues from pesticide applicators and users of downstream products should provide EPA with confidence that the short term effects driving EPA's concern – respiratory irritation and dermal sensitization – are not being seen from current uses and use rates.

The Task Force hopes that, after reviewing these comments, EPA will agree that all existing uses and use rates of DCOIT meet the FIFRA risk/benefit standard for continued registration and that no mitigation is needed beyond that being voluntarily undertaken. The Task Force is committed to good product stewardship. In the event EPA is interested in discussing further mitigation measures, notwithstanding the Task Force's continued strong belief that such measures are not necessary, the Task Force will be willing to engage with EPA to discuss possible measures that will provide additional safety margins while at the same time preserving the viability of IT biocides for existing uses. This includes the importance of ensuring use rates can be sufficiently high to provide effectiveness and that mitigation measures are not so burdensome as to make certain uses technically or economically impracticable.

In conclusion, the Task Force requests that EPA reissue the DCOIT DRA incorporating the corrections, changes, and information presented in these comments. EPA should not proceed with issuing a Proposed Interim Decision or any risk mitigation for DCOIT until the record is corrected and stakeholders are provided another opportunity to comment.

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APPENDICES

APPENDIX A

Benefits of Selected Uses for Isothiazolinones

Pursuant to the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), EPA must regulate biocides such that they "will not generally cause unreasonable adverse effects to man or the environment, taking into account the economic…, social and environmental costs and benefits of the use of any pesticide...". The benefits to the economic and social aspects of society must therefore be balanced against the risks to human health and the environment. Accordingly, **EPA must be able to understand and then assess the benefits of a substance in order to properly regulate under FIFRA**. To assist EPA with this effort, the IT Task Force is providing below a detailed assessment of the benefits of ITs by industry segment, to highlight the importance of this active ingredient in a number of downstream industries.

This document highlights the long history of isothiazolinones (ITs) and their benefits in multiple industries, applications, and use scenarios. This class of chemistries has broad applicability -- from controlling microbial growth in cooling tower water systems to extending the shelf life of everyday household products. ITs offer benefits in the form of short- and long-term material preservation as well as an important function in industrial processes. Most notably, a replacement of the class of ITs is a significant challenge as no other class of actives provides the same level of benefits.

The following are the IT use categories detailed in this paper: 1) Wood Preservation, 2) Polymer Dispersions and Solutions; 3) Paints and Coatings; 4) Building Materials; 5) Household, Industrial and Institutional Products; 6) In-can preservation; 7) Metalworking fluids; 8) Cooling Towers. From this list, it is evident that the uses and applications for ITs are disparate and wide ranging, and accordingly the benefits they provide have wide ranging impact. This information is of utmost importance to ensure that both the evaluation EPA performs and the conclusions EPA reaches are supported by information that is robust, fully informed, and satisfies FIFRA requirements

I. ITs and Material Preservation

ITs are primarily used in material preservation. The use of antimicrobials in material preservation has grown increasingly important as volatile organic chemicals (VOCs), once in common usage, were replaced in numerous applications by aqueous systems. The switch to aqueous- based solvents, while providing an improvement to environmental and human health protection, has led to a growing need for biological control. The conditions for most VOC-containing products articles were not conducive to microbial growth; however, aqueous-based systems are fertile ground for biological contaminant growth. The contaminants must be controlled to assure that the products are safe and remain safe for use.

Material preservative uses will generally fall into one of three categories of intended durations of protection: (1) short-term preservation of raw materials, (2) in-can preservation of products prior

to use; and (3) long-term preservation of finished articles and materials to prolong useful life. Examples of the types of materials needing short-term protection include slurries, latex emulsions, pigment dispersion, sapstain, and polymer emulsions. Examples of the types of products needing in-can preservation include latex paints, coatings, adhesives, waxes, polishes, liquid soaps, detergents, other consumer products, printing inks, etc. Lastly, long-term preservation is essential to extend the period of product utility and can be found in paper coatings, applied paint films, and metalworking fluids. ITs are effective in all three categories of material preservation.

Material preservation is critical to the conservation of energy and natural resources, as it significantly reduces waste generation. Consequently, material preservatives are not only valuable, but critical to society, serving to protect public health, preserve manufacturing processes, and extend the life cycle of products.

Section I below addresses the benefits of ITs as a material preservative (applying the three categories of preservation discussed above) and Section II discusses the benefits of ITs in an industrial process.

A. Short-term Preservation of Raw Materials

1. Wood Preservation

Biocides play a significant role in addressing contaminants such as mold, mildew and sapstain in timber. Mold, mildew, and sapstain increase the wood's ability to hold water, thus increasing chances of decay. Depending on the length of mold and mildew control desired based on the sector at-issue, different biocides are chosen. Biocides also play a role in sapstain control of timber through use of specially formulated wood treatment products to protect peeled logs from mold and stain causing fungi.

Biocides play an important role in wood stability and product sustainability. ITs are the primary choice to prevent mold in the wood preservation market. They are compatible with wood preservative formulations and are effective at low use levels. ITs are often used alone or in combination with other anti-sapstain fungicides for mold control. CMIT/MIT and OIT are often used for short-term control due to their cost effectiveness for freshly cut wood in transit and their effectiveness in protecting pressure treated lumber from mold growth during storage, transportation, and while sitting in consumer stores/lumber yards.

The benefit of using ITs in the wood industry is significant. They:

- reduce the need to kiln dry wood, which saves on energy consumption required to operate kilns;
- expand applications of wood, since treatment can abate decay;
- allow for treated wood to be stored at lumberyards or on jobsites for a longer period of time without the threat of mold growth. This results in less spoilage of wood and returns from dealers;

- promote a healthier environment for construction sites as little to no mold exists on the wood; and
- improve the durability of timber, which contributes to forest conservation.

2. Polymer Dispersions and Solutions

Polymer or latex dispersions, emulsions, and slurries are raw materials used to manufacture many products, including adhesives, paints, coatings, non-woven fabrics, paper, printing inks, and construction materials. As synthetic polymer systems have moved away from free monomer and VOC based formulations, water-based polymer formulations have been substituted and are widely used. As discussed above the need for effective preservation in water-based formulations is necessary to protect the formulations.

For more than 40 years, ITs have been central in successful preservation of water-based polymer dispersions and solutions. ITs are versatile across the full spectrum of polymer dispersions and solutions. They have been adapted for use in acrylics, water-reducible and water-dispersible alkyds, polyurethane dispersions and polymers derived from 'natural' biological origin.

Selection of the correct IT combination, as well as the level required for each individual application, depends on the physicochemical characteristics and solid-to-water content of the various water-based polymeric systems. Longevity of preservation and stability of the ITs in application are further considerations, all requiring careful selection of the best IT preservative package. Many polymers are produced, stored and transported in bulk, requiring a good balance of short-to-long-term stability.

CMIT/MIT and BIT, are especially suitable for in-can preservation of water-based polymer dispersions and solutions because of their favorable water solubility. Their electrophilic character ensures that they all target the critical components of bacterial and fungal metabolic pathways, ensuring that a broad spectrum of organisms are killed and more importantly, unable to reproduce.

Just as end use products must be free of contaminants, the products that serve as the building blocks for paints and coatings, adhesives, construction materials, and so on must also be free of contaminants. ITs play a valuable role in stabilizing and preserving polymer products. Subsequently, manufacturers of polymer products benefit from cost-saving opportunities as well as a reduction in potential wasted materials.

B. In-Can Preservation of Products Prior to Use

1. Paints and Coatings

The paint and coatings industries are substantial, mature industries in the United States, which incorporate antimicrobial biocides into their manufacturing processes. In the last 30 years, paint and coating formulations have undergone a metamorphosis, transitioning away from solvent-borne paints toward waterborne paints. In addition, paints and coatings are comprised of more

naturally derived raw materials. These changes in paint and coating formulations – while improvements – create a more hospitable environment for microorganisms.

Collectively, paints and coatings, like many commodity products, are subject to microbial attack and decay. Microbes have the ability to contaminate these products and affect their appearance and function throughout all stages of product manufacture. Common raw materials such as latexes, clays and talcs to name a few, offer the perfect environment for the growth of bacteria and fungi, are included in the formulation of these products. Many raw materials for these industries are derived from fossil fuels as well as minerals and agricultural-based materials. Materials such as water, thickeners, latexes, clays, talcs and other natural raw materials (e.g. soy) are themselves preserved with antimicrobial pesticides in order to preserve their service life and enable their safe passage under a variety of harsh conditions to their manufacturing destinations. Further, the manufacture of paints and coatings are not conducted under sterile conditions, and the introduction of harmful microbes can occur at any point in the manufacturing process. Introduction of antimicrobial pesticides into the finished product therefore increases manufacturing efficiency: constant surface sanitation within facilities is not required. Furthermore, inclusion of antimicrobial pesticides ensures products are adequately protected from microbial decay during their transport and retail storage life.

Consequently, all paints require preservation. A majority of paint is treated with an in-can preservative or biocide. Some others are treated with a dry-film preservative or biocide. The selection of a biocide is governed by a variety of factors making the process for selecting a preservative rather complicated. Paint manufacturers are often reluctant to alter the preservative package in a paint formulation because effective alternatives to ITs as a preservative in paints does not exist.

In particular, CMIT/MIT and BIT protect paints and coatings from contamination and subsequent degradation by bacteria and fungi in the wet state. Additionally, ITs—such as OIT and DCOIT—protect the dried paint/coating against degradation by mold and mildew in interior applications (especially bathrooms), as well as against mold and certain algae in exterior applications.

A key benefit of IT use in paints and coating is the role these chemistries play in product integrity. Foul paint is a wasted paint. Consequently, wasted paint leads to expensive waste management costs. Leftover paint can also contain volatile organic compounds, mercury and lead. Of all household hazardous wastes, paint is the single most voluminous and expensive material that many local governments collect and manage. ITs serve to minimize waste generation associated with waste transportation and disposal.

The benefits of ITs in paints and coatings is best understood through a report titled "Life-Cycle Assessment of Architectural Coatings Considering Different Preservative Scenarios" conducted by the American Coatings Association (ACA) in 2018.[35] The study found that replacing,

[35] Available at https://www.paint.org/coatingstech-magazine/articles/life-cycle-assessment-of-architectural-coatings/ (last accessed Nov. 20, 2020).

reducing or eliminating certain preservatives such as ITs, impacts the coatings overall sustainability profile. Specifically, global warming potential, acidification, eutrophication, ozone depletion and smog formation increased 50% to 400% when compared to use of ITs as the preservative. ITs provide the paint and coatings industry with longevity, a critical element of sustainability. Without them, high-VOC solvent-based formulations would be much more prevalent, contributing to the large-scale issue of climate change. From prolonging the life cycle, to protecting products from scratches, rust, and corrosion, ITs stand at the foundation of the paint and coatings industry.

2. Building Materials (including Adhesives and Sealants)

The building materials industry includes adhesives and sealants, grouts, caulks, concrete admixtures and solutions, and gypsum slurries for wallboard. These products are essential inputs to the $2.0-trillion U.S. construction industry, which employs 6.6 million people.[36]

Since water is a primary component of each of these end uses, building materials are susceptible to microbial attack. Biocides play a role in ensuring the structural stability and sustainability of building materials, while also contributing to maintaining the aesthetic integrity of the product (e.g., protecting the color of grout).

Building materials can become contaminated by a wide range of microorganisms (bacteria, yeasts and molds) and hence benefit from the use of ITs, which have the broadest spectrum of efficacy across organism types. In addition, construction adhesives and sealants benefit from the addition of fungicides and algaecides which prevent biological establishment on cured products in service. Cured products discolored by algae or mold and mildew affect customer satisfaction and confidence in the treated product integrity. Here, ITs such as OIT and DCOIT have proven to be very effective (on their own or in combination with additional dry-film preservative chemistries).

In order to maintain the longevity of building materials, ITs must be used in the formulation of adhesives, sealants, grouts, caulks and other concrete admixtures and solutions. With respect to building materials, ITs serve as the ideal preservative due to their favorable solubility profile, electrophilic character, and their compatibility with other products.

3. Household, Industrial, and Institutional Products (HI&I)

The COVID 19 pandemic highlighted the importance of hygienic control in the home. Routine and frequent cleaning with a variety of household products has become commonplace. Products such as disinfectants, laundry and dishwashing detergents, surface cleansers, and polishes of all types contain high percentages of water as well as various organic or polymeric components. Water encourages microbial growth, and organic or polymeric components serve as a food source for harmful organisms. Trends toward neutral pH, low VOC content, and more sustainable ingredients such as polyglucosides and plant-based surfactants can make it more

[36] Economic Census: Summary Statistics for the U.S., States, and Selected Geographies: 2017.

difficult to effectively preserve products. Biocide preservatives are designed to control microbes over time and protect product integrity along the supply chain, until fully used by an end user.

As with the other end-use segments, multiple factors must be weighed in the selection of the proper preservative. Matrix compatibility, use levels, pH, co-formulant compatibility, length of control, price, toxicology, and environmental impact all play significant roles in preservative selection. Cleaning product formulators take care to responsibly create products using levels of preservatives that are efficacious and compliant with EPA-approved ranges. As a result of the demanding performance requirements and public preferences, HI&I formulators have few registered options beyond ITs to utilize in cleaning applications. ITs are highly effective at low ppm levels compared to other preservatives, have favorable formulation properties, and have been used extensively in this area for 25 years.

For background, alternatives to ITs in HI&I products has been thoroughly explored. Alternative preservation systems such as organic acids, which have limited EPA registrations, have restricted application, as they need to be formulated to an acidic pH to be effective. Many cleaning products are formulated between 8-11pH, which provides the optimal cleaning profile. Low pH cleaning products are not suitable for many of the surfaces found in US households as they can cause surface damage. Organic acids may not provide broad-spectrum protection in every formulation as they are primarily fungicides and cannot control bacteria on their own. The use levels for organic acids are typically 4-10%, significantly higher than ITs depending on the combinations used. The use levels for ITs are typically less than 0.05%. Manufacturers have also used high pH in an attempt to control microbial growth without IT-type chemistries; however, this only proved to be a temporary solution with organisms adapting, leading to spoilage within 6 months to a year.

The cost of an ineffectively preserved product will render products useless, resulting in product recalls from store shelves, warehouses, and homes, generating a large quantity of waste. Additionally, the products would need to be reworked or replaced, which would require additional use of materials, such as ingredients and packaging. Detergent recalls can cost anywhere from $1-10 million including removal of product off shelf, cleaning plants, disposal, replacement, QA investigation and other related activities. In HI&I products, IT chemistries are readily biodegradable, non-toxic intermediates that do not bio-accumulate. Notably, ITs are accepted for use within EPA's Safer Choice Program, which is critical for many household product formulators because this acceptance demonstrates a commitment to the environment.

4. In-Can Preservation of Agricultural Products

As seen in a number of other industries, the formulation of crop protection products also migrated from solvent-based to water-based formulated products. Existing agricultural pesticides have intrinsically lower solvent solubility, which requires harsher solvents to achieve practical formulations. These formulations tend to be more acutely hazardous. Solvent based systems are not compatible with existing application equipment requiring more safeguards and ultimately cost to applicators. Solvent based formulations are impractical for consumer ready-to-use due to their odor and safety hazard; therefore, the industry's movement to water-based systems was inevitable.

Water-based systems were made possible only by the implementation of ITs in the preservation of agricultural products. This positive shift in the formulation of in-can preservation of agricultural products has led to lower environmental and worker/applicator/user impact. Benefits of such systems include:

- Water-based systems address the general undesirability of introducing large amounts of solvent and surfactants into soil and the environment.
- Water-based systems enable response to and compliance with (a) state-driven volatile organic carbon (VOC) regulations; (b) air permits; (c) application in non-attainment areas (with respect to ambient air quality standards); and (d) California Prop 65 (among others).
- Increasing use of biologically based pesticide alternatives (including options in organic agriculture) inherently requires or strongly favors water-based formulations.
- The increasing emphasis and reliance on seed-treatments to minimize the quantity of applied pesticide and exposure to those pesticides (including the applicator, air quality, downstream consumer, etc.) requires water-based application systems to achieve seed safety.
- Water-based formulations overcome the impracticality of granular systems on large-scale farms typical in the US, because handling of liquid concentrates is inherently preferable compared to large-scale handling of solid products.
- Protection of application mixtures ensures that diluted product not immediately applied does not spoil, which would require equipment cleaning and waste disposal, and lead to financial loss.
- Customers prefer water-based systems, conferring a market advantage to these safer systems.

Water-based systems also minimize or eliminate the need to transport solvents by road or rail, in favor of supplying water to the formulation facility by water line or well. Production, distribution, and use of water-based pesticide formulations under aseptic conditions is impractical or impossible; hence, preservation of water-based products is an absolute requirement. Preservatives are needed primarily (but not exclusively) to protect the rheological modifier (*e.g.*., xanthan gum and related bio-based polymers) required to effectively suspend active ingredients (AIs). Accurate metering and application of the formulated product requires uniform and stable formulations that do not settle and have a uniform assay of AI throughout the bulk of the product as sold and as diluted for use in the field.

Biocides prevent damage to packaging, such as swelling, hence avoiding leakage and spillage. Likewise, biocide usage serves to prevent a loss of production, prevent the need for disposal of unrecoverable/spoiled product and reduce waste. Additionally, effective use of biocides is essential to field application of pesticides, avoiding plugging of nozzles and fouling of application equipment. Importantly, biocides act to prevent microbial and pathogen contamination, protecting both workers and the public. The industry faces very limited options for preservation of formulated systems. In the same vein, the industry sees significant levels of emerging microbial resistance to alternatives to ITs (e.g. parabens). Accordingly, any loss of preservative options has a disproportionate impact by eliminating potential ingredients needed to

maintain product safety and quality in combination preservative packages. On a global scale, very limited options are accepted and available for preservative packages. Loss of IT-based options would have a disproportionate impact by limiting trade and the opportunity to sell products that are developed and produced in the US to the international market.

Bacterial and fungal contamination can occur in aqueous formulations, severely curtailing their effectiveness on target pests in the field. CMIT/MIT and BIT are particularly suited for this use because of the broad spectrum of activity and longevity of control in this environment. In addition, residue tolerances or exemptions from tolerance are required for all ingredients, both active and inert, of formulated pesticides registered for application to food crops, either pre-plant, pre-harvest, or post-harvest. These ITs are unique within the preservative portfolio for their food-use tolerance exemptions under 40 CFR §180.920. They can also be used in products formulated for nonfood-uses.

The importance of the IT chemistries to the agricultural and specialty pesticide sectors was highlighted during the worldwide BIT shortage in 2018, caused by regulatory restrictions and industrial accidents that disrupted BIT production in China. This required short-term regulatory modifications by EPA, agreed upon both by the IT registrants and the agricultural crop protection community, to find substitutes. This situation highlights the limited number of antimicrobial tools available to this industry. The only alternatives having tolerance exemptions that permit use on food crops are the other IT products, CMIT/MIT and MIT. Additional restrictions on this class of chemicals would devastate the agricultural sector, since there are no other cost-effective antimicrobial alternatives that have the necessary tolerance exemptions.

C. Long-Term Preservation

1. Metalworking Fluids

Metalworking fluids (MWF) are engineered materials that facilitate metalworking processes. MWFs provide cooling (at tool-workpiece interface); lubrication (at interface); corrosion protection (workpiece, tool, fixtures and machinery); and a liquid stream to flush away chips & swarf [metal fines] (especially during cutting & grinding of metal). These functions are important for several reasons including protection of tool life, protection of metallurgy of the part, and maintaining the integrity and safety of the industry process. Metalworking fluids include:

- straight oils (contain no water)
    - Sold as concentrates and diluted with water at point-of-use (coolants):
- soluble oils (oil in water emulsions)
- semi-synthetic fluids (oil-in-water micro- emulsions)
- synthetic fluids (contain no oil, strictly water-based with synthetic organics)

Biocides are a critical constituent of MWFs as they control microbial growth. MWFs fluids provide almost ideal conditions for bacterial growth since they are rich in nutrients and water and are most often used at 20-40 degrees C. In addition, there are many sources of microbes which continually inoculate these fluids: water used to dilute the fluids both initially and evaporation

make-up (especially from other than potable sources), airborne contamination, soils (from parts, shoes, floor sweepings etc.) and humans themselves (skin, sweat, spittle etc.).

Unmanaged microbial growth can lead to costly loss of productivity, causing down-time due to production disruptions, maintenance, etc., worker dissatisfaction with work environment and re-work of finished parts (corrosion, surface blemishes on metal parts, etc.). Microbial deterioration of the performance additives in the fluid can lead to a significant reduction in the useful life of the machine tool. In some industries the machine tool can be the costliest component of the process. The annual adverse economic effect of uncontrolled microbial growth can be valued in the tens of millions of dollars.[37]

Proper biological control can extend a MWF's life significantly: from a useful life of a few weeks for a system containing no microbial control, to a year or more if properly maintained. This results not only in a dramatic reduction of material to be waste treated, but a significant savings in system clean out labor and down-time costs. Since system clean out requires microbial clean out as well, there is less frequent exposure to the higher concentrations of antimicrobials required to effectively clean the system in order to prevent an almost instant reinoculation of the replacement fluid.

A primary route of exposure to microbes in the metalworking environment is from the aerosols generated during the machining process. These microbes can cause a spectrum of issues from minor coughs to severe pulmonary disorders such as hypersensitivity pneumonitis (HP).

There is a limited number of biocides that can be used in the preservation of MWFs because the MWF environment is harsh and biocide longevity is low. ITs are one of only a few biocides that can be used for MWFs. Multiple criteria account for their selection and use: shop conditions, health and safety, performance, compatibility, life-cycle considerations and, most importantly, cost to the end user.

With lower ITs treatment rates, systems utilizing MWFs need to be replaced more frequently, with tanks emptied and refilled, and safe disposal of the contaminated MWFs. Utilizing a 20,000-gallon diluted MWF system for demonstration purposes, the estimated annual cost with waste treatment of tank-side ITs is around $1.335 per gallon based on existing data. Without the use of ITs, the cost per system gallon becomes $4.83, incorporating replacement and more frequent disposal of MWFs. Brief, informal surveys of MWF industry members reflect the use of around 66,000,000 gallons of annual use in the United States. Elimination of ITs as an effective microbial control would result in an annual economic impact of around $230,670,000 just to keep existing systems working, let alone ancillary costs to the health and safety of workers.

In summary, microbes have a tremendous economic impact on metalworking fluid system operations. Proper management of the metalworking fluid can have a significant positive impact on all affected aspects: health and safety, economics and environmental. ITs extend the useful life of these fluids and mitigate potential health problems associated with their occupational use.

[37] Metalworking Fluids, 2nd Edition, Jerry P. Byers, 2006, p 196.

II. IT and Industrial Processes

It is impossible to overstate the importance of microbiological control in all water systems. The primary problems arising in water systems are fouling and biofouling. Fouling generally is the presence of unwanted surface-attached materials on submerged materials. Biofouling, in simplest terms, is the attachment of any organism to submerged surfaces. Controlling fouling is essential to the integrity of water systems and the primary goal of water treatment.

Industrial uses of water include boiler-makeup, processing, product treatment and cleaning, cooling, and many others. Industrial water consumption is a significant factor in production costs, and has become important as part of ongoing efforts to conserve limited water resources. For example, throughout the chemical industry, more than 80 percent of water used for cooling and steam generation is recycled. Therefore, in-plant water recycling and wastewater treatment systems are significant parts of the industrial process for many facilities. There is always a need to control water quality to prevent corrosion, scale deposits and slime formation, which has become even more important with the growing use of recycled water or recovered wastewaters. Additionally, there is a need to control water quality and prevent the colonization of pathogenic bacteria such as *Legionella,* which left uncontrolled can have devastating effects on public health.

A. Cooling Tower Water Systems

Cooling towers are necessary in a wide range of industrial processes, including steel mills, chemical plants, manufacturing and food facilities, large buildings, refineries, and electric utilities. Cooling water systems control temperatures and pressures by transferring heat from hot process fluids into the cooling water, which carries the heat away. As this happens, the cooling water heats up and must be either cooled before it can be used again or replaced with fresh makeup water.

This habitat is an ideal medium for the growth of microorganisms. Left uncontrolled, this growth contributes to fouling, corrosion, and scale. Microbial slimes are masses of microscopic organisms and their waste products. These slime layers are usually sticky and effective in trapping foulants present in the bulk water. Microorganisms floating freely in the water are known as “planktonic.”

There are diverse organism groups that could be present in cooling water systems, including: *Pseudomonas, Aerobacter, Flavobacterium, Bacillus, Thiobacillus, Legionella, Desulfovibrio, Sphaerotilus, Stigeoclonium, Oscilltoria, Lyngbya, Aspergillus, Penicillium, Sacchromyces, Torula* and *Lenzites spp*.

Cooling towers use fans to move air through recirculating water systems that produce water vapor and droplets that may be present in the environment. Design factors are employed to reduce or eliminate the potential for drift of water vapor and droplets. Nonetheless, use of ITs in these recirculating water systems is essential for public-health protection, in addition to the

significant benefits derived from protecting equipment, maintaining recycled water quality, conserving energy and resources, and overall efficiency.

Preventing waterborne illnesses from exposure to sources other than drinking water is an important public-health issue. The CDC publishes annual reports on waterborne illnesses that result from drinking water, recreational waters (pools and spas), and other water sources. The reports are instructive about the continuing need for vigilance in controlling waterborne microbiological contaminants.

APPENDIX B

Information on Materials Preservation Formulations, Container Sizes, and Packaging

Table 1: Registered End-Use Materials Preservative Formulations Containing ITs					
Formulation	**Percent Active Ingredient**				
	BIT	**DCOIT**	**OIT**	**CMIT/MIT**	**MIT**
Powder	None	None	20%	1.5%	None
Liquid	1.1 – 41.9%	4 - 30 %	0.3% - 46.5%	0.52 - 28%	2.5 – 50%
Other	NA	10% (plastic pellet) 98.5% (fused solid)	10% (plastic pellet)	7% (granular)	NA

Table 2: Packaging of Liquid Registered End-Use Materials Preservatives					
Container Type	**BIT**	**DCOIT**	**OIT**	**CMIT/MIT**	**MIT**
1, 2.5- or 5-gallon jugs	YES	YES	YES	YES	YES
15, 30- or 55-gallon drums	YES	YES	YES	YES	YES
250 to 500-gallon totes	YES	YES	YES	YES	YES
Bulk containers >500 gallons	None	None	None	Yes	None

Table 3: Packaging of Pour Solid Registered End-Use Materials Preservatives					
Container Type	**BIT**	**DCOIT**	**OIT**	**CMIT/MIT**	**MIT**
Powder Formulations					
Bags ≤ 50 lbs	NA	NA	NA	NA	NA
>50 to 200 lb drums	NA	NA	55 lb drum	77 lb plastic keg	NA
Bulk bags	NA	NA	NA	125 kg bag G	NA
Granular Formulations					
Containers < 50 lbs	NA	NA	NA	5-gal pail G 20 lb box G	NA

Note: The range of active ingredient covers a variety of registered end-use products, including products where the isothiazolinone is one of several active ingredients.

APPENDIX C

Response by the Isothiazolinone Task Force to Inhalation Risk Assessment

3(2H)-isothiazolinone, 4,5-dichloro-2-octyl (DCOIT)

REGISTRATION REVIEW DRAFT RISK ASSESSMENT FOR DCOIT

PC Code: 128101
DP Barcode: D455507, 455508, 456952
Decision No.: 558151, 558152, 558144
Docket No: EPA-HQ-OPP- 2014-0403

Regulatory Action: Registration Review Case No.: 5023
Risk Assessment Type: DRA
CAS No.: 64359-81-3

April 6, 2020

RESPONSE BY THE ISOTHIAZOLINONE TASK FORCE TO INHALATION RISK ASSESSMENT

December 2020

I. BACKGROUND

(2H)-isothiazolone, 4,5-dichloro-2-octyl (DCOIT) is one of several cyclic compounds which belong to the isothiazolinone chemical group. It is registered as a materials preservative (for incorporation into products such as building materials, adhesives, coatings, resin emulsions, paints, and various other specialty industrial products), a microbiocide (for use in pulp/papermills, cooling water systems, air washer systems, industrial process waters, can warmers and brewery pasteurizers), a wood preservative (to treat wood products), and as an antifoulant paint and polymer (for commercial and naval use). There are 30 active registrations, including 3 manufacturing-use products and 27 end-use products.

In 2020, the Antimicrobial Division (AD) of the Office of Pesticide Program (OPP) of the U.S Environmental Protection Agency (USEPA) conducted an occupational and residential exposure risk assessment of DCOIT for registration review. In this assessment, the Agency identified risk of concern via the dermal and the inhalation routes for occupational and residential handlers and for residential post application exposure (USEPA, 2020a).

II. RESPONSE BY THE ISOTHIAZOLINONE (ITF)

In this submission, the ITF presents their responses to EPA's 2020 draft risk assessment specifically with regard to risk via inhalation exposure of DCOIT from residential and occupational uses.

III. EXPOSURE PROFILE

A. Use Pattern

As of January 14, 2020 there are 30 products (three are manufacture use products or MUPs) registered for uses for incorporation into products such as building materials, adhesives, coatings, resin emulsions, paints, and various other specialty industrial products (as a preservative); and, as a microbiocide in pulp/paper mills, cooling water systems, industrial process waters, can warmers and brewery pasteurizers, and air washer systems. The compound is also registered as a wood preservative to treat wood products (seasoned/unseasoned forest products and various finished wood products), as an antifoulant paint for commercial and naval use, and as an antifoulant polymer for use by the US Navy. One MUP (EPA Reg # 707-224) specifies several uses (sapstain, in-can preservatives for laundry detergents and household cleaners, oil injection waters, metal working fluid preservatives, fuel preservation) that have no registered end-use product labels, application rates or directions for use (USEPA, 2020a).

B. Residential Exposure

1. Residential Handler Exposure

There is the potential for residential handler exposure when using paints that are preserved with DCOIT. These exposures are anticipated to be of a short-term duration because painting is conducted for a few days per year.

2. Residential Post-Application Exposure

There is no potential for residential post-application exposures via the inhalation route to materials that are preserved with DCOIT other than paints.

C. Occupational Exposure

There is the potential for occupational handler exposure when DCOIT is used to preserve materials such as paints and plastics, exposure during the commercial application of DCOIT antifoulant paints to large vessels such as cargo ships, cruise ships and large pleasure boats (*i.e.*, mega yachts) and during use of DCOIT to pressure treat wood.

IV. TOXICITY PROFILE OF DCOIT

The toxicity profile of DCOIT is presented in Appendix 1. Acute toxicity data show that it is moderately toxic by the oral route (Toxicity Category III); however, because the irritation and corrosivity of the chemical, waivers were granted for the acute dermal, acute inhalation, primary eye irritation and primary skin irritation studies and were assigned to Toxicity category I. DCOIT is a dermal sensitizer.

Subchronic oral toxicity studies conducted in both rats and dogs show systemic effects after repeated oral administration. In rats following oral (gavage) administration, DCOIT caused decreases in body weight, food and water consumptions, alterations in several hematology/blood chemistry parameters and histopathological lesions in the forestomach. In dogs dietary administration of DCOIT resulted decreases in body weight gain and food consumptions, alterations in clinical chemistry parameters, decrease in thymus weights and macroscopical and microscopical changes in the thymus glands. Following subchronic inhalation exposure, treatment-related the histopathological alterations observed in the nose (min/mild subacute inflammation and transitional respiratory epithelial and goblet cell hyperplasia), larynx (chronic-active inflammation and hyperplasia of the squamous and cuboidal epithelium), and lungs (acute inflammation and goblet cell hyperplasia at high-dose). There is no evidence of increased quantitative or qualitative susceptibility following *in utero* exposure to rats and rabbits in the developmental toxicity studies and following pre- and post-natal exposure to rats for two generations. Waivers were granted for chronic toxicity/carcinogenicity studies. DCOIT was negative in a battery of *in vivo* and *in vitro* assays (USEPA, 2015).

Although their toxicological effects are qualitatively similar, the isothiazolinone biocides differ in potency with No Observed Adverse Effect Levels (NOAELs) and Lowest Observed Adverse Effect Levels (LOAELs) varying across the groups for these effects, EPA concluded that it was appropriate to consider the toxicity databases of the chemicals as one group due to the similarity of the toxicity profiles, including the adverse effect of dermal sensitization. For risk assessment purposes, chemical-specific data are used when available. When chemical-specific data are not available, the most conservative endpoint for which there are data from other isothiazolinones is used (USEPA, 2020b).

V. POINTS OF DEPARTURE AND TOXICITY ENDPOINTS USED BY USEPA.

The PODs and endpoints used in EPA's draft assessment for DCOIT is presented in Table 1.

Table 1. Points of Departure Used in the 2020 Draft Risk Assessment (USEPA, 2020).

Exposure Scenario	Points of Departure (PODs)	RfD, PAD, LOC and UFs	Study/Toxicological Effects
Acute Dietary (All populations, including infants, children and females 13 to 49)	NOAEL=500 mg/kg/day	UF= 30 UF_A= 3X UF_H= 3X UF_L= 3X FQPA SF= 1X aRfD = 17 mg/kg/day aPAD =17 mg/kg/day	Acute oral (gavage) – rat (MRID 42977701)) LOAEL = 500 mg/kg/day based Clinical signs of toxicity and death beginning at 750 mg/kg (one male rat). Signs of toxicity included yellow viscous material in the intestines, reddened stomach mucosa, somnolence, tremor, and diarrhea. There was no mortality at 500 mg/kg. Diarrhea and mucus in stool were observed at 500 mg/kg.
Chronic Dietary (All populations	Offspring NOAEL=30 mg/kg/day	UF =100 UF_A= 10X UF_H= 10X FQPA SF= 1X cRfD = 0.3 mg/kg/day cPAD =0.3 mg/kg/day	Two generation reproduction Toxicity Study in Rats (MRID 45756501) LOAEL (reproductive P/F1 62-88 [M], 67-93[F] mg/kg/day based on significantly delayed vaginal opening (35.1 days vs. 31.9 days in control) and preputial separation (46.2 days vs. 42.9 days in control) in F1 offspring.
Incidental Oral (Short- and Intermediate-Term)	NOAEL=30 mg/kg/day	Residential LOC for MOE = 100 UFA =10 UFH = 10 FQPA SF= 1X	Two generation reproduction Toxicity Study in Rats (MRID 45756501) Same study as used for chronic dietary above.
Dermal (All Durations)	EC3 = 0.023% (5.8 μg/cm^2)	Residential and Occupational LOC = 30 UF_A = 100 UF_H = 100	Average EC3 = 0.023%, Confidence Interval = 0.020 to 0.026% Based on Model 4 from Hirota et al. 2015: DPRA + h-CLAT + KeratinoSens
Inhalation (Short- and Intermediate-Term)	NOAEC = 0.02 mg/m^3 HEC = 0.0045 mg/m^3	Residential and Occupational LOC = MOE of 10 UFA = 3 UFH = 3 FQPA SF= 1	**Bridged using DCOIT 90-Day inhalation study** (MRID 43487501) LOAEC = 0.63 mg/m^3 , based on the histopathological alterations observed in the nose (min/mild subacute inflammation and transitional respiratory epithelial and goblet cell hyperplasia), larynx (chronic-active inflammation and hyperplasia of the squamous and cuboidal epithelium), and lungs (acute inflammation and goblet cell hyperplasia at high-dose).
Inhalation (Long- Term)		Residential and Occupational LOC = MOE of 30 UFA = 3 UFH = 3 UF_D = 3 FQPA SF= 1	

NOAEL= No Observable Adverse Effect Level. LOAEL= Lowest Observable Adverse Effect Level. aRfD= acute reference dose; aPAD = acute population adjusted dose; cRfD= chronic reference dose; cPAD = chronic population adjusted dose. UF = uncertainty factor, LOC = level-of-concern. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_L = LOAEL to NOAEL extrapolation. UF_D = Duration Adjustment. MOE = Margin of Exposure. Inhalation Uncertainty Factor lowered by a factor of 10 due to use of HEC.

VI. EVALUATION OF THE RISK ASSESSMENT BY ITF.

ITF does not concur with EPA's selection of the 90-Day inhalation study in rats with DCPOIT and the use of the NOAEL of 0.02 mg/m3 (HEC = 0.0045 mg/m^3) for inhalation exposure risk assessment based on the following considerations.

1. EPA's Use of the DCOIT Inhalation Study

In a repeated exposure inhalation toxicity study (MRID 43487501), groups (32/sex/concentration) Crl:CD (SD) were exposed nose-only to DCOIT (32.6%) in o-xylene (vehicle) at analytical concentrations of 0.02, 0.63 and 6.72 mg/m^3, 6 hours/day, 5 days/week for 13 weeks. The aerosol particle size gave a mean mass median diameter (MMAD) of 1.4 μm, the mean geometric standard deviation (GSD) was 4.6 and the mean respirable fraction (RF) was73%. Parameters evaluated included survival, clinical signs of toxicity, body weight, hematology and clinical chemistry, organ weight, gross necropsy, and histopathology. Half of the animals from each group were necropsied at the end of the thirteen-week exposure period, five/sex/ group were necropsied at six months and the remaining animals were necropsied at the end of a one-year recovery period. Histopathological examination of rats sacrificed at 13-week and after a 6-month recovery period was conducted but not on rats sacrificed after the 1-year recovery period.

Dose levels for this study were selected based on the results of two range finding studies:

- In a 2-week range finding study, groups of Crl:CD:SD rats (5/sex/dose) were exposed nose-only to DCOIT at concentrations of 0.0 (air control), 0.05, 0.32, 1.9 and 7.1 mg/m^3, 6 hours/day, 5 days/week for 14-days. The MMD was 1.4 μm, the GSD was 5.3 and the mean RF was 71%. Rats exposed to 1.9 and 7,1mg/m^3 showed signs of respiratory irritation (slight respiratory noise, dyspnea and bradypnea). No differences in mean body weight gains were seen in any group. Blood analysis showed no differences in blood chemistry parameters for any group. Necropsy revealed increased number of lungs with red or tan foci, red or grey discoloration in all treated groups. No differences were seen in lung weights for any animal at the end of the two-week exposure period.
- Due to minimal toxicity seen in the two week range-finding study, groups of Crl:(CD): SD rats (4/sex/dose) were exposed to DCOIT in o-xylene at concentrations of 0.0 (air control) and 13.7 mg/m^3, 6 hours/day, 5 days/week for 3-weeks. Another group was exposed to o-xylene at 7.8 mg/m^3 on the same schedule. The MMD was 1.4 um, the GSD was 6.4 and the RF was 71 %. The animals exposed to 13.7 mg/m^3 showed signs of respiratory irritation (slight respiratory noise, dyspnea, bradypnea, apnea and nasal discharge) and decreased body weight gains. Animals exposed to o-xylene(vehicle control) showed signs of slight respiratory noise. Necropsy revealed an increase in lung observations (red foci or darkened throughout) in treated rats. An increase in lung weights relative to the body weight was seen in the animals exposed to o-xylene. This was judged to be a result of exposure to the vehicle. When adjusting for the effect of the vehicle on the lungs, the test material exposed animals showed no increase in lung eights relative to the body weights.

Based on the data from the range-finding studies, concentrations of 0.01, 0.7 and 7.0 mg/m^3 were selected for the 13-week study. It is noted that there is a 700-fold dose spread between the low and the mid dose levels and the study director provided no rationale for this disparity in the doses selection. Analytically determined chamber concentrations were 0.02, 0.63 and 6.72 mg/m^3 and

there is a 31.5-fold difference between the low and the mid dose. Therefore, the selected concentrations were not spaced appropriately to produce a concentration-response curve.
There were no treatment-related mortality. Clinical signs of toxicity characterized as rales manifested primarily in the respiratory tract of rats only at the high dose (6.72 mg/m^3). Body weight gains were decreased by 16% and 14% in males and females, respectively during the exposure period. Animals regained their weights upon cessation of treatment. Treatment had no adverse effects on hematology and clinical chemistry parameters, organ weights or gross necropsy at any dose level. At 13-weeks, histopathological lesions were limited to the nose, larynx, and lungs at 0.63 and 6.72 mg/m^3 dose groups. No. histopathological lesions were seen at the low dose (0.02 mg/m^3). Treatment-related lesions were seen in the nose (minimal/mild subacute inflammation and transitional respiratory epithelial and goblet cell hyperplasia); larynx (chronic-active inflammation and hyperplasia of the squamous and cuboidal epithelium); and lungs (acute inflammation and goblet cell hyperplasia at the high-dose). At the six-month necropsy recovery was seen in all tissues, and the lungs no longer showed signs of histopathological lesions. The authors concluded that recovery began upon cessation of treatment. The NOAEL is 0.02 mg/m^3 and the LOAEL is 0.63 mg/m^3 based on the portal-of-entry effects in the nose, larynx, and lungs. The disparity (31.5-fold) between the low and the mid dose points to the uncertainty in the experimental results that are due to characteristics of the study design such as dose selection and dose spacing and the reliability of the findings for risk assessment.

2. Toxicologic Significance of the Respiratory Tract Lesions

The portal-of-entry (POE) effects observed in the 13-week study are typical irritation-type effects caused by the isothiazolinones and are common findings in rats exposed to respiratory tract irritants (Jiang et al.,1986; Feron *et al*., 1986). However, the study authors did not provide criteria that was considered in identifying adverse, nonadverse, and adaptive findings. The decision about whether or not test article–related effects (or a group of related effects) in a non- clinical study are considered adverse or non- adverse should be unambiguously stated and justified in study reports.

This study was conducted in 1989 and the nomenclature, descriptors and the criteria for grading utilized in the diagnosis of the respiratory tract lesions have "progressed" since that time. The Society of Toxicologic Pathologist (STP) developed a standardized nomenclature of proliferative lesions in the respiratory tract (Schwartz *et al*, 1994). In 204, Crissman *et al.* developed best practice guidelines for more clear reporting of the findings in nonclinical toxicology studies. The European Society of Toxicological Pathology(ESTP) coordinated an international expert workshop to characterize the concept of ''adversity'' more clearly in current practice to particular organ or lesion types. Use of nomenclature such as that endorsed by the STP and clear, cogent communication of the findings and their interpretation are essential for proper assessment of the observed effects in a toxicity study (Kerlin *et al* 2016; Palazi et al). In 2016, STP provided guidance on determining and communicating adversity ''Is it adverse, adaptive or artifact?'' using case studies involving both clinical pathology and anatomic pathology (Pandiri *et al*., 2016).

Goblet cell hyperplasia should be considered adverse if it was presumed at a magnitude able to impair respiratory function (e.g., mucus in the airway), olfactory function (e.g. loss of olfactory epithelium) or ability to clear particulate matter (e.g., loss of ciliation). In the DCOIT study, there was no impairment of the respiratory function since there was no treatment-related mortality, there was no alteration of the olfactory epithelium at the mid dose and there was no loss of cilia at any dose. Goblet cell hyperplasia of the lungs was seen only at the high dose and was reversible after the 6-month recovery period. Lewis *et al* (1992) reported that some of the effects seen in toxicity

studies that do not causes any functional impairment in the test organism should not be considered to be adverse. Therefore, in this case, since there was no functional impairment of the lung function and the lesions were reversible, the goblet cell hyperplasia should be regarded as non-adverse.

Goblet cell hyperplasia of the nasal turbinate is rather nonspecific and is observed in studies of a wide variety of chemicals and aerosols such as high concentrations of cigarette smoke, industrial chemicals, atmospheric pollutants, and, occasionally, pharmaceuticals (Gopinath *et al.*, 1987). A wide variety of exogenous materials through physical or chemical irritation would be expected to stimulate the production of more mucus by goblet cells. This response may be an attempt to increase the efficiency of muco-ciliary clearance by the respiratory tract (Burger *et al*., 1989). Goblet cell hyperplasia has been seen in both short and long-term studies. It is thought to be an adaptive response to irritant exposure and is not considered a preneoplastic change (NTP).

In the DCOIT study, laryngeal epithelial hyperplasia at the base of the epiglottis and vocal folds was minimal at 0.63 mg/m^3 and moderate at 6.72 mg/m^3. According to Osimitz *et al* 2007, minimal, focal epithelial changes of the larynx epithelium predominantly occurring at the base of the epiglottis should be given the descriptive term of an "epithelial alteration" as the morphologic criteria of a "laryngeal squamous metaplasia" are not completely met. The laryngeal hyperplasia was reversible and was not seen at 0.63 mg/m^3 after the 6-month.

In the DCOIT study. laryngeal squamous metaplasia was minimal to mild at 0.63 mg/m3 and minimal to mild at 6.72 mg/m^3. There was no evidence of impairment of the laryngeal or respiratory function in rats at these dose levels since there was no treatment-related systemic toxicity (e.g., no mortality, alterations in clinical pathology, organ weight, gross necropsy). After a 6-month recovery period, no laryngeal squamous metaplasia was seen in either sex at the mid dose and recovery was seen in both sexes at the high dose. Lewis (1991) reported that cases of minimal to slight focal "laryngeal squamous metaplasia" that are not observed diffusely are addressed as "non-adverse" as well. They are not considered precancerous lesions. Kaufman *et al* (2009) recommended that minimal to mild focal laryngeal metaplasia in the absence of other related effects does not impair lung function and thus should not be considered as "adverse".

Furthermore, the occurrence of squamous metaplasia in short-term studies does not necessarily equate to future problems in long-term studies. Lack of progression in either severity or into proliferative changes in the studies with ozone and cobalt (Boorman *et al.*, 1994; NTP, 1998) are in agreement with conclusions drawn by Burger *et al*. (1989) and Lewis (1991) that laryngeal squamous metaplasia is an adaptive change due to a local irritation that typically does not progress to neoplasm. Lewis (1991) also reported that "squamous metaplasia" was reversible in nature with all compounds examined and reported in this paper.

The squamous metaplasia of the respiratory epithelium overlaying the ventral gland is the most common induced lesion in rodents. This epithelial change in the larynx of rodents is an issue of frequent discussions with respect to its biological and toxicological significance. Burger *et al* (1989) reported that exposure to aerosols may cause transitional epithelium at the base of the epiglottis in rats to change into squamous epithelium. Weber *et al*. (2009) reported also spontaneously occurring squamous metaplasia in male Wistar rats from 13-weekinhalation studies and in longer lasting studies. It was stated that the most common induced lesion consisted of squamous metaplasia of the originally ventral respiratory epithelium overlaying the ventral gland and this induced squamous metaplasia does not differ from the spontaneously occurring squamous metaplasia. In an oncogenicity study, the incidence was at 20.0% in control animals without any

indication of dysplasia or hyperplasia. The lesion is considered to be indicative of the especially high sensitivity of the rodent larynx to any mild irritant and cannot be regarded to be of adverse nature as long it occurs focally at this location and is low in degree (Rosenbruch and Kaufmann, 2008). In the ESTP international workshop the experts found that many induced spontaneous minimal laryngeal lesions reported in inhalation exposure studies does not fulfil the criteria of a completed "squamous metaplasia" (WHO nomenclature citation) (Kaufmann et al., 2009).

The ETSP Workshop also concluded that although inhalation exposure of rodents to non-genotoxic compounds (isothiazolinones are non-genotoxic) may induce laryngeal squamous metaplasia, there is no reported cases of tumor induction in the larynx with a non-genotoxic compound. Therefore, for non-genotoxic compounds, laryngeal squamous metaplasia by itself should not be regarded as a precancerous lesion (Kaufman et al. 20009)

In the DCOIT study, clinical signs and decreased body-weight gain were seen only at the high dose and the rats gained weight upon cessation of treatment. There was no effects on clinical pathology, organ weight or gross necropsy. After a 6-month recovery period, there was reversibility in both incidence and severity and there was no progression over time. According to Osimitz *et al*. 2007 these factors indicate that the laryngeal squamous metaplasia is an adaptive response and should not be considered to be indicative of significant human risk. *The authors further concluded that squamous metaplasia of the rodent larynx is not a relevant toxicological endpoint for quantitative risk assessment.*

In summary, treatment-related findings were primarily limited to the portal-of-entry effects in the nose, larynx, and lungs at the mid and high dose groups. The study authors did not provide criteria that was considered in identifying adverse, nonadverse, and adaptive findings. The decision about whether or not test article–related effects (or a group of related effects) in a non- clinical study are considered adverse or non- adverse should be unambiguously stated and justified in study reports. Consequently, there is potential for changes in the conclusion of the respiratory tract lesions observed if the current nomenclature, descriptors, and the criteria for grading the severity are utilized in the evaluation of the DCOIT inhalation toxicity study. Such an evaluation can make differences in interpretation and characterization of "adverse" vs. "non-adverse effects. In deciding whether an effect is adverse or adaptive, it is less likely to be considered adverse if the effects do not induce alterations in the tissues or organs, the effects are transient, or the effect is limited. Thus, there is low confidence in design, conduct and results of this study due to the poor dose selection which failed to produce a concentration-response curve as well as in the qualitative and quantitative analysis of the pathology findings which could impact the decision-making process of arriving at NOAEC/LOAEC values.

3. <u>Concern for Offspring Toxicity</u>

In the two-generation reproduction study, offspring toxicity manifested through clinical signs, decreased pup weight, and decreased organ weight (spleen and/or thymus) and/or delays in vaginal opening and preputial separation secondary to reduced body weight. in the F1 pups. This endpoint was used for dietary (chronic) and non-dietary (incidental oral) risk assessments. When there is a concern for effects in the fetuses in a developmental toxicity study or in the offspring in a reproductive toxicity, OPP' guidance is to use these effects as the endpoint of concern for inhalation risk assessment since the route-specific inhalation study does not evaluate the potential for developmental and reproduction endpoints (USEPA, 1998). Example of OPP's precedence in

using the two-generation reproduction study for inhalation exposure risk assessment is presented below and in Appendix 2.

- Clothianidin (USEPA,2017): *A route-specific inhalation toxicity study was available. In the two-generation reproduction study with rats, offspring toxicity manifested as decreased body weight gains, delayed sexual maturation, decreased thymus weights in F1 pups, and increased stillbirths in both offspring generations. An oral POD from this study was selected since the available inhalation toxicity study did not evaluate the potential for reproductive/offspring toxicity.*

VII. PODs AND ENDPOINTS PROPOSED FOR INHALATION RISK ASESSMENT

ITF is proposing to use the two-generation reproduction study for assessing risk via the inhalation route for all exposure durations (short-, intermediate-, and long-term).

All Durations (Short-, Intermediate-, and Long-Term)

Study: Tw-Generation Reproduction – Rat (MRID 45756501)

Proposed NOAEL: 30 mg/kg/day

Executive Summary In a two-generation reproduction study (MRID 457565-01), male and female Crl:CD®BR rats received diets containing DCOIT (100.3% a.i.) at dose levels of 0, 200, 800, or 3200 ppm for two generations. These doses were equivalent to 0, 16-20, 62-88, and 235 mg/kg/day in males during premating and 0, 18-21, 67-93, and 259 mg/kg/day in females during premating). Significant offspring mortality at 3200 ppm caused an insufficient number of pups available to produce a second generation; consequently, all surviving 3200-ppm offspring were euthanized prior to sexual maturation. An additional treatment group of 400 ppm (equivalent to 30-39 mg/kg/day in males and 33-41 mg/kg/day in females) and a concurrent control group were initiated. P1 and P2 males and females were 6 or 3 weeks of age, respectively, when dosing was initiated and were exposed to the test article for at least 10 weeks prior to mating. Treatment continued until termination and included gestation and lactation periods.

Parental effects seen at 800 and 3200 ppm dose groups included clinical signs of toxicity (paleness), significantly decreased body weights (3200-ppm P1 and 800-ppm P2 animals), significantly decreased body weight gain (3200-ppm P1 and 800-ppm P2 animals), significantly decreased body weight and body weight gain in 3200-ppm P1 females during gestation, significantly decreased body weight in 3200-ppm P1 females during lactation, and significantly decreased mean food consumption (3200-ppm P1 and 800-ppm P2 animals). Other findings included treatment-related hyperplasia and hyperkeratosis of the non-glandular stomach of P1 (both sexes) and an increased incidence of hypertrophy/vacuolation of the zona glomerulosa of the adrenal cortex was both sexes of the P1 animals.

For parental toxicity, the NOAEL is 400 ppm (30-39 mg/kg/day for males and (33-41mg/kg/day, for females) and the LOAEL is 800 ppm (62-88 for males and 67-93 mg/kg/day for females) based on decreased bodyweight and body weight gain (and food consumption in the females).

There was no evidence of reproductive toxicity. No treatment-related adverse effects were seen on estrus cycling, male and female mating and fertility, gestation index, gestation length or in the number of pups per litter, or pup viability. For reproductive toxicity, the NOAEL is 3200 ppm (235 mg/kg/day in males and 259 mg/kg/day in females; the highest dose tested. A LOAEL was not established for reproductive toxicity.

Offspring toxicity seen at 800- and 3200 ppm doses included: clinical signs of toxicity (paleness and distended abdomens in 3200-ppm F1 pups); significant decrease in pup weight (800ppm F1 and F2 animals and 3200-ppm F1 animals); significant gross necropsy findings (3200 and 800ppm F1 pups); significant decreases in absolute and relative mean thymus (800 and 3200 ppm) and spleen (400, 800, and 3200 ppm) weights in F1 males; significant decreases in mean thymus weights (800 and 3200 ppm) in F1 females; and significant decreases in absolute and relative mean thymus weights (400 and 800 ppm) in F2 animals (both sexes). The mean age at preputial separation was delayed at 800 ppm and the mean age at vaginal opening delayed at 400 and 800 ppm in F1 offspring. There was no treatment related effect on anogenital distance in the F2 offspring. Additionally, at 3200 ppm, the lactation index for P1 females was significantly decreased due to the significant increase in the number of litters with liveborn pups that did not survive to postnatal day (PND) 21.Concurrently, the number of pups dying, missing and/or cannibalized significantly increased on PND 5-21 and 0-21, contributing to the decreased lactation index.

For offspring toxicity, the NOAEL is 200 ppm (16-20 in males and 18-21 mg/kg/day in females) and the offspring toxicity LOAEL is 400 ppm (62-88 in males and 67-93 mg/kg/day in females)based on based on decreased absolute and relative spleen and thymus weight and significantly delayed vaginal opening and preputial separation secondary to reduced body weight in F1 offspring.

Comments about Study/Endpoint: Offspring toxicity manifested through clinical signs, decreased pup weight, and decreased organ weight (spleen and/or thymus) and/or delays in vaginal opening and preputial separation secondary to reduced body weights. In the inhalation study, the portal-of-entry effects seen at the end of the study (13-weeks) were reversible (at 6-month) upon cessation of exposure. In contrast, reversibility has not been demonstrated for all of the effects observed in the reproduction study and reversibility is generally not considered for pubertal markers. Because these effects are adverse and potentially not reversible, they should be considered for human health risk assessment (ILSI, 1998). The reproduction study is selected because the potential for reproductive and/or offspring toxicity is not evaluated in a route-specific (inhalation) study. The treatment regimen in the reproduction study is appropriate for all exposure durations and is protective of systemic toxicity seen in the oral subchronic and developmental toxicity studies in the DCOIT database.

Level of Concern (LOC): **Target MOE of 1000**.

A route-specific study should be determined to be not appropriate for risk assessment when there are potential risk for a specific endpoint(s) identified in the oral studies which are not evaluated in the route-specific study. Under this condition, the appropriate oral study with the most sensitive endpoint will be used for risk assessment. Under this situation, when an oral NOAEL based on the sensitive endpoint is selected, typically the LOC is a target MOE of 100 which includes the conventional Uncertainty Factors (UFs) of 10x for inter-species extrapolation and 10x for intra-species extrapolation. However, in this situation, even though an oral NOAEL is proposed for inhalation risk assessment, a target MOE of 1000 is proposed. The oral study chosen identified significant developmental effects (decreased pup body weight and decreased spleen and/or thymus weight and delayed sexual maturation secondary to reduced pup weight) in the offspring (the most sensitive endpoint) via the oral route. In contrast, an inhalation study identified only portal-of-entry effects, related to the irritant properties of the chemical which are reversible. Thus,

uncertainty is increased for the potential reproductive toxicity via the inhalation route. **This uncertainty is addressed by the target MOE of 1000 which includes the conventional 100 and a 10x Modifying Factor.**

The EPA's RfD Technical Panel states that in addition to the standard uncertainty factors, an additional modifying factor (MF) may also be applied when scientific there are uncertainties in the study chosen or database that are not explicitly addressed by the standard UFs. It is further stated that use of the factor depends principally on professional judgment and assessment (USEPA, 2002a).

EPA's IRIS has used variable MFs for establishing RfD for chromium III, chromium VI, nitrite, and a RfC for acetonitrile (USEPA, 2002b).

Oral Equivalent Dose: An oral NOAEL is selected for this risk assessment. For risk assessment, the exposure from the inhalation route has to be calculated to an internal dose. Therefore, the inhalation NOAEC express as mg/m^3 is transferred to an internal dose (mg/kg/day). For such conversion, the following formula is used:

Conversion of inhalation concentration (mg/L/day) to an oral equivalent dose (mg/kg/day)

$$\text{Oral dose (mg/kg/day)} = \frac{\text{mg/L/day x A x RV x D}}{\text{BW}}$$

Where:
A= Inhalation: oral absorption ration, default 1
RV= Respiratory Volume (L/hour), 10.26 L/hr (Default Respiratory Volume for Sprague-Dawley rats)
D= Duration of daily exposure (6-hour exposure)
BW= Body weight, 0.236 kg(average weight for male and female Sprague-Dawley rats).

The NOAEC/LOAEC for the DCOIT inhalation study is translated to an oral equivalent dose as shown below:

DCOIT Inhalation Study	
NOAEC = 0.02 mg/m^3 or 0.00002 mg/L	**LOAEC = 0.63 mg/m^3** or 0.00063 mg/L
$\frac{0.00002 \times 1 \times 10.26 \times 6}{0.236}$ = **0.0052 mg/kg/day**	$\frac{0.00063 \times 1 \times 10.26 \times 6}{0.236}$ = **0.164 mg/kg/day**

POD: Use of the 1000 UF to the NOAEL of 30 mg/kg/day results in a POD of **0.03 mg/kg/day** (30 ÷ *1000*).

Rationale for the Proposed POD and Endpoint: In the DCOIT inhalation study, treatment-related findings were primarily limited to the portal-of-entry effects in the nose, larynx, and lungs at the mid and high dose groups. There was a 31.5-fold difference between the low and the mid dose; therefore, the selected concentrations were not spaced appropriately to produce a concentration-response curve. The study authors did not provide criteria that was considered in identifying adverse, nonadverse, and adaptive findings. The decision about whether or not test article–related effects (or a group of related effects) in a non- clinical study are considered adverse or non- adverse should be unambiguously stated and justified in study reports. Consequently, there is potential for changes in the conclusion of the respiratory tract lesions observed if the current nomenclature, descriptors, and the criteria for grading the severity are utilized in the evaluation of the DCOIT inhalation toxicity study. Such an evaluation can make differences in interpretation and characterization of "adverse" vs. "non-adverse effects. In deciding whether an effect is adverse or adaptive, it is less likely to be considered adverse if the effects do not induce alterations in the

tissues or organs, the effects are transient, or the effect is limited. Thus, there is low confidence in design, conduct and results of this study due to the poor dose selection and data analysis which could impact the decision-making process of arriving at NOAEC/LOAEC values.

More importantly, the developmental effects observed in the male and female offspring following oral exposure are adverse effects. They signify a more sensitive endpoints for risk assessment than the local irritation effects at the port of entry seen via inhalation exposure which are reversible upon cessation of exposure. Since the inhalation study is not designed to evaluate the potential for offspring toxicity there is residual uncertainty for this endpoint via the inhalation route. This uncertainty is addressed by the application of an additional 10x Modifying Factor. This POD will be protective of female workers and home makers of childbearing age and their infants as well as the male population since adversity in offspring can manifest through either sex. This POD will also be protective of the respiratory tract irritation seen in the inhalation study.

Impact of the Proposed POD on Other Isothiazolinones: Subchronic inhalation toxicity studies were conducted with CMIT/MIT, and OIT.

In a 13-week inhalation toxicity study in rats with *CMIT/MIT*, treatment-related POE effects were the nasal turbinates at 1.15 mg/m^3, the LOAEL. An oral equivalent dose of 0.30 mg/kg/day.

In a 13-week inhalation toxicity study in rats with *OIT*, treatment-related effects were irritation to the respiratory tract and lesion in the nasal cavity and lungs at 6.3 mg/m^3, the LOAEL. An oral equivalent of 1.64 mg/kg/day.

The proposed oral POD (0.03 mg/kg/day) is protective of the concern for: 1) the portal-of-entry effects seen at 0.164 mg/kg/day in the DCOIT inhalation study; 2) portal-of-entry effects seen at 0.3 mg/kg/day with CMIT/MIT and at 1.64 mg/kg/day with OIT inhalation toxicity studies; and 3) as well as the systemic, developmental and reproductive toxicity seen at doses greater than 30 mg/kg/day in the DCOIT data base. Thus, the proposed POD will not underestimate risk from residential and occupational inhalation exposure to DCOIT.

VIII. PROPOSED REVISED RISK ASSESSMENT BY THE ITF

A. Residential Exposure

There is the potential for residential handler exposure when applying paints and stains that are preserved with DCOIT. Exposures are anticipated to be of short-term in duration.

1. Residential Handler Inhalation Exposure

The assumption that a residential Do-It Yourself consumer (DIY) painter would apply three 5-gallon cans (15 gallons) of paint using an airless sprayer is not realistic. Information obtained from several paint manufacturers by the American Coatings Association indicate that it is very uncommon for the DIY painter to use an airless sprayer. Airless sprayers are used to paint large indoor or outdoor surface areas, and because of the spray mist, indoor airless spraying is done in vacant rooms or buildings. This would not be a typical use scenario for a DIY consumer painter. Additionally, although larger surface areas for painting can be found outdoors, the paint industry indicated that it is less common for DIY paint to be applied outdoors. Only under special circumstances would an airless sprayer be used outdoors by a consumer, for example painting a fence outdoors. Even in that situation, it is anticipated that less than 10 gallons of paint would be

used by a consumer in a day. Another respondent stated that past market research indicated that the DIY consumer purchased an average of 3 gallons for a project, not the 15 gallons used in the airless spraying assessment. Additionally, only 17% of DIY consumers purchase an airless sprayer. From this information, it can be concluded that even if a DIY consumer used an airless sprayer for their project, they would use far less than 15 gallons a day. **As such, a more realistic, yet conservative, default of 10 gallons of paint was used to assess risks to consumer painters using airless sprayers**.

There is a discord in the mopping risk assessment between how the unit exposures are normalized using the study data and default input parameter of amount of mopping cleaner used per day. This was resolved by assuming that 10% of the EPA daily default amount of cleaner used for mopping ends up on the floors. **Therefore, 0.1 gallons, instead of 1 gallon, was used in the revised residential risk assessment.**

The revised residential handler inhalation MOEs using an oral POD is presented below. There are no risks of concern since the MOEs are greater than the LOC of 1000 for the appropriate (short term) exposure duration of concern.

Table 1: ITF Revised Residential Handler Inhalation MOEs for DCOIT.

Paint Application Scenario	Application Rate[A]	Gallons of Paint Applied per Day	Amount a.i. Handled[C] (lb/day)	Unit Exposure (mg/lb a.i.)	Inhalation Exposure[F] (mg/kg/day)	MOE[G, H] LOC=1000
Airless Spray	2000 ppm a.i.	10[B]	0.20	0.993[D]	0.0024	**12,500**
Brush/Roller		2[B]	0.040	0.0078[E]	0.000004	**7,500,000**

I. The maximum use rate.
J. A more realistic, yet conservative, default of 10 gallons of paint is used.
K. .Amount of a.i. Handled (lb/day) = Application Rate (ppm/1,000,000) x Amount Product Applied (gal) x Product Density (10 lb/gal)
L. AEATF II airless sprayer study (MRID 50879401).
M. AEATF II brush/roller study (MRID 50521701).
N. Inhalation Exposure (mg/kg/day) = Amount a.i. Handled (lb/day) x Unit Exposure (mg/lb a.i.) x 100% absorption ÷ bw (80 kg)
O. MOE = Inhalation NOAEL (mg/kg/day) / Inhalation Exposure (mg/kg/day).
P. Inhalation NOAEL: oral POD 30 mg/kg/day, LOC=1000

B. Occupational Exposure

There is the potential for occupational handler exposure when DCOIT is used to preserve materials such as paints and plastics. There is also the potential for occupational handler exposure when using paints that are preserved with DCOIT.

1. Occupational Handler Inhalation Exposure

In assessing the addition of liquid preservatives to a paint manufacturing process, instead of using the total conventional liquid pour dermal and inhalation unit exposures from the AEATF II liquid pour study (MRID 48917401) for assessing the addition of liquid preservatives to a paint manufacturing process, only the exposure data based on the combined conventional pour and reduced-splash Groups 2 and 3 should be used. The reason for this is that Group 1 contained 3 monitoring events (MEs 2, 4, and 6) which were done by pouring from 24 , 32, and 64 oz bottles which are not reflective of the larger jugs and open buckets that would be used to manually transfer liquid preservatives in an industrial setting. Removing these three MEs results in an inhalation

exposure of 0.0014 mg/lb ai compared to the unit exposures of 0.0017 mg/lb. Even with this refinement, the AEATF II liquid pour data provide a conservative estimate of exposure for paint/adhesives manufacturing because several of the monitoring events required test subjects to first pour into small measuring cups which increased the potential for exposure and, while might be reflective of janitorial activities, this is not reflective of use patterns in large scale industrial operations.

The other issue is that the default of 45 gallons of diluted cleaning solution used for mopping seems excessively high. The AEATF II mop study which was designed to represent the total amount of time spent mopping during a work shift and EPA's review of the study confirms this. The upper-end time spent mopping in the study was 1.5 hours/day, with, on average, subjects using 4 buckets of solution for mopping. The industrial janitorial mop buckets used in the study were 35-quart (8.75 gallons) capacity. Assuming the buckets are 75% full, this would mean 6.5 gallons per bucket, multiplied by 4 buckets results in 26 gallons per day, not 45 gallons.

The IT Task Force has revised the mopping risk assessment to adjust for the discord between the unit exposures and the default assumption for amount of mopping solution used per day. **The revised risk assessments were done using 4.5 gallons of cleaner instead of 45 gallons.** This is 10% of the Agency's default. It is assumed that 10% of the mopping solution ends up on the floor (for every 45 gallons of solution used in a day, 4.5 gallons ends up on the floor).

The revised occupational handler inhalation MOEs using an oral POD is presented below. There are no risks of concern since the MOEs are greater than the LOC of 1000 for the appropriate (short-term) exposure duration of concern.

Table 2: ITF Revised Occupational Handler Inhalation MOEs for DCOIT

Scenario	Application Rate[A]	Amount of Product Applied or Material Treated per Day[B]	Amount a.i. Handled (lb/day)[C]	Inhalation Unit Exposure (mg/lb a.i.)	Inhalation [G]Exposure (mg/kg/day)	MOE[H,I] LOC= 1000
Open pour liquids for paint preservation	2,000 ppm a.i.	20,000 lbs of paint	40	**0.0014[D]**	0.0007	**42,000**
Airless Spray Application of Paint	2,000 ppm a.i.	500 lb of paint	1.0	0.993[E]	0.0124	**2,400**
Brush/Roller Paint Application		50 lb of paint	0.10	0.0078[F]	0.000001	**3,000,000**

J. The application rates are the maximum rates from the labels.
K. Standard assumptions used for occupational exposure assessments of AD chemicals.
L. Amount of a.i. Handled (lb/day) = Application Rate (ppm/1,000,000) x Amount Product Applied or Treated (lbs).
M. Unit exposure from AEATF II liquid pour study (MRID 48917401). **Groups 2 and 3 only.**
N. AEATF II airless sprayer study (MRID 50879401).
O. AEATF II brush/roller study (MRID 50521701).
P. Inhalation Exposure (mg/kg/day) = Amount a.i. Handled (lb/day) x Unit Exposure (mg/kg/day) x 100 absorption÷ bw (kg).
Q. MOE = Inhalation NOAEL (mg/kg/day) / Inhalation Exposure (mg/kg/day).
1. **Inhalation NOAEL: oral POD 30 mg/kg/day (All durations).**

2. Shipyard Painter Exposures to DCOIT in Antifoulant Paints

Occupational handler exposures are anticipated to occur via inhalation during the commercial application of DCOIT antifoulant paints to large vessels such as cargo ships, cruise ships and large pleasure boats (*i.e.*, mega yachts) and are anticipated to be intermediate term in duration.

Since the inhalation POD selected for DCOIT is based on an oral study, the measured air concentrations (mg/m^3) have been converted to an adult daily dose (mg/kg/day) using the following formula: This formula was used by the Agency (USEPA, 2020; DP No. D430516)

- Measured inhalation concentration (mg/m^3) x (0.001 m^3/L) x (16.7 L/in) x (60 min/hr) x 8 hrs/day) x 1 /69 kg

There is a risk of concern for Trial B spray men with an MOE of 107, however, this risk is mitigated with a PF 10 respirator with a MOE of 1,071 which is above the LOC of 1000. There are no risks of concern for other job functions since the MOEs range from 1200 to 15,000.

Table 3. Shipyard Painters MOE for DCOIT							
Trial[A]	**Job**	**Amount ZPT Handled During Study[B] (lb a.i./day)**	**Amount DCOIT Handled[C] (lb a.i./day)**	**Inhalation Unit Exposure[D] (µg/m³/lb a.i.)**	**Inhalation Exposure[E]**		**MOE[F] (LOC = 1000)**
					(mg/m³)	**(mg/kg/day)**	
ACD	Spray Man	18.3	25.2	8.27	0.208	0.0241	**1,244**
	Line Tender	14.8	20.4	3.12	0.064	0.0074	**4,054**
	Pot Man	26.6	36.6	0.44	0.016	0.0019	**15,789**
B	Spray Man	11.8	16.2	149	2.41	0.2799	107
	Spray Man	11.8	16.2	149	2.41	0.2799	**1,071[g]**
	Line Tender	11.8	16.2	12.7	0.206	0.0239	**1,255**
	Pot Man	23.5	32.3	1.57	0.051	0.0059	**5,084**

A. Plastic tenting with a small exhaust fan was used during Trial B to prevent overspray.
B. Average values for each job. Amounts handled for multiple cycles per day were added together.
C. Amount DCOIT handled = Amount a.i. handled during study *(5.23 % DCOIT / 3.8% ZPT in study paint)
D. Are the Estimated Arithmetic Average (AMm) inhalation unit exposure values taken from Table 23 of the EPA risk assessment.
E. Inhalation Exposure (mg/m³) = Amount DCOIT Handled (lb a.i./day) * Inhalation Unit Exposure (µg/m³/lb a.i.) * 0.001 mg/µg
F. Inhalation Exposure converted to an adult daily dose (mg/kg/day) [(mg/m³) x (0.001 m³/L) x (16.7 L/min) x (60 min/hr) x (8 hrs/day) x 1/69 kg)]
G. PF10 Inhalation MOE = Inhalation MOE / Protection Factor for respirator (10). PF10 respirator is assumed to reduce inhalation exposure by 90% *"Occupational Pesticide Handler Unit Exposure Surrogate Reference Table – March 2020"*
https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/exposure-surrogate-reference-table-pesticide-risk
Inhalation NOAEL: oral POD 30 mg/kg/day (All durations).

3. Pressure Treatment Worker Exposures to DCOIT

Occupational handler exposures are anticipated to occur via inhalation during use of DCOIT to pressure treat wood. These exposures are anticipated to be intermediate to long term in duration.

There are no risks of concern for treatment operator or wood handler since the MOEs are greater than the LOC of 1000.

Table 4. Pressure Treatment Workers Inhalation MOEs for DCOIT						
Job Function	**Application RateA (% a.i.)**	**Fraction a.i.[B]**	**Inhalation Unit Exposure[C] (µg/m³/fraction a.i.)**	**Inhalation Exposure[D]**		**MOE[G] (LOC = 1000)**
				(mg/m³) [E]	**(mg/kg/day)[F]**	
Treatment Operator	0.69	0.0069	3.0	0.000021	0.0000024	12,500,000
Wood Handler			11.6	0.00024	0.0000017	17,600,000

A. Application rate is for utility poles, cross arms and bridge timber listed on EPA Reg No. 83997-13.
B. Fraction a.i. = Application Rate (% a.i.) / 100
C. Estimated Arithmetic Average (AMm) for the 8- hour TWA total inhalable fraction unit exposures from the AEATF II Pressure I. Treatment Exposure Study (MRID 49434501) for Sites ABDE.
E. Inhalation Exposure (mg/m³) = Fraction a.i. * Inhalation Unit Exposure (mg/m³/fraction a.i.) * 0.001 mg/µg
F Inhalation Exposure converted to an adult daily dose (mg/kg/day) [(mg/m³) x (0.001 m³/L) x (16.7 L/min) x (60 min/hr) x (8 hrs/day) x 1/69 kg)]
G .**Inhalation NOAEL= oral POD 30 mg/kg/day (all durations)**

IX. CONCLUSIONS

(i) Residential Exposure

There are no risks of concern via inhalation exposure for residential handlers when applying paints using an airless spray (MOE = 12,500) or brush/roller (MOE=7,500,000) since the MOEs are greater than EPA's level of concern (LOC) which is a target MOE of 1000.

(ii) Occupational Exposure

There are no risks of concern via inhalation exposure for occupational handlers during open pour liquids for paint preservation (MOE=35,000) and when applying paints using an airless spray (MOE = 2,400) or brush/roller (MOE=3,000,000) since the MOEs are greater than the LOC of 1000.

There are no risks of concern via inhalation exposure for shipyard workers spraying antifoulant paint except for Trial B's job function of "sprayman" with an MOE of 107 which is mitigated with a PF10 respirator resulting in an acceptable MOE 1071 which is greater than the LOC of 1000.
There are no risks of concern via inhalation exposure for pressure treatment workers, The inhalation MOEs for treatment operators and wood handlers are greater than the LOC of 1000.

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APPENDIX 1

Table A1. Toxicity Profile for (DCOIT)

Guideline No. Study Type	MRID No. (year)/ Classification /Doses	Results
Non-Guideline 28-Day Oral Toxicity-Rat	MRID 42214903 0, 20, 100, or 500 mg/kg/day Acceptable	NOAEL = 20 mg/kg LOAEL = 100 mg/kg/day**,** based on increased water consumption, hematological/clinical chemistry changes, histopathological lesions in stomach and small intestine.
870.3100 90-Day Oral Toxicity-Rat	MRID 43471603 0, 100, 500,1000, and 4000 ppm (equivalent to 0, 6.2/7.2, 32.5/36.7, 60.7/74.7,248.2/278.4 mg/kg/day in M/F Acceptable	NOAEL = 32.5 mg/kg/day (M)/ 36.7 mg/kg/day (F) LOAEL = 60.7 mg/kg/day (M)/74.7 mg/kg/day (F) Based on microscopic forestomach lesions, decreased triglyceride levels
870.3150 90-Day Oral Toxicity-Dog	MRID 45747201 0, 100, 300 and 1500 ppm (3.4/3.4, 10.2/10.1, 47.5/45.9 mg/kg/day) Acceptable	NOAEL = 10.2 mg/kg/day (M)/10.1 mg/kg/day (F) LOAEL = 47.5 mg/kg/day (M)/ 25.9 mg/kg/day (F) Based on decreased hematology and clinical chemistry parameters
870.3450 90-Day Inhalation Toxicity- Rat	MRID 43487501 0.02, 0.63, 6.72 mg/m3, 6 hours per day, 5 days per week. Acceptable	NOAEC = 0.02 mg/m^3 LOAEC = 0.63 mg/m^3 **(**HEC=0.0045 mg/m^3**),** based on histological alterations of the nose, larynx, and lungs. HEC = NOAEC * (6-hour animal/8 -hour human) * RDDR (0.30 for ET effects, BW= 420 grams, MMAD = 1.4 um, GSD = 4.6)
870.3700a PrenatalDevelopmental Toxicity- Rat	MRID 43471604 0, 1, 10, 30, and 100 mg/kg from days 6-15 of gestation. Acceptable	<u>Maternal</u> NOAEL= 10 mg/kg/day LOAEL = 30 mg/kg/day, based on decreased food consumption, scant feces, soft feces, or diarrhea. <u>Developmental toxicity</u> NOAEL = 30 mg/kg/day LOAEL = 100, based on increased incidence of wavy ribs (21 fetuses in 11 litters vs. 2 fetuses from 1litter in control).
870.3700a 2-Generationre Reproduction Toxicity-Rat	MRID 45756501 0, 200, 800, or 3200 ppm (0, 16-20, 62-88, and 235 m/k/d (M) and 0, 18-21, 67-93,259 m/k/d (F) Acceptable	<u>Parental</u> NOAEL= 33-39 mg/kg/day (M)/ 33-41 mg/kg/day (F). LOAEL = 62-88 mg/kg/day (M)/ 67-93 mg/kg/day (F) based on decreased body weight/weight gain <u>Reproductive</u> NOAEL= 235 mg/kg/day (M)s and 259 mg/kg/day (F) LOAEL = Not established <u>Offspring</u> NOAEL= 33-39 mg/kg/day (M)/ 33-41 mg/kg/day (F LOAEL = 62-88 mg/kg/day (M)/ 67-93 mg/kg/day (F)

Table A1. Toxicity Profile for (DCOIT)		
Guideline No. Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.5100 Bacterial Reverse Mutation Test	MRID 43935708 N-octylisothiazolone S.typhimurium . strains at Strain: TA98, TA100, TA102, TA1535, and TA 1537 . 0.064, 0.32, 1.6, 1.875,3.75, 7.5, 8, 15, 30, or40 ug/plate (+/-S9) Acceptable	Negative, with or without S9 activation.
870.5300 *In Vitro* Mammalian Cell Gene Mutation Test HGPRT Locus in Cultured Chinese Hamster Ovary (CHO) Cells With and Without Metabolic Activation	RH-287 administered in two independent assays Non-S9 activated doses of 0.025, 0.05, 0.1, 0.2,0.4, 0.5, and 0.75ug/ml S9 activated doses of 2.5, 5.0, 6.0, 8.0, 9.0,10 or 15 ug/m. Acceptable	Negative, with or without S9 activation.
870.5375 *In vitro* Mammalian Chromosomal Aberration Assay	RH-287 exposed at non-activated doses of 0.3, 0.6, 0r 0.7 ug/ml (initial trial) or 0.5, 0.6, or 0.7 ug/ml (confirmatory trial) S9 activated doses of 6, 7, or 8 ug/ml (both trials) Acceptable	Negative, with or without S9 activation.
870.5395 *In vivo* Sister Chromatid Exchanges Micronucleus Assay in CD-1 Mouse Bone Marrow Cells.	MRID 43471608 RH-287 administered orally at 32.5, 162.5 or 325 mg/kg Unacceptable	A slight dose—related increase in MPEs was observed in the males of the mid- and high-dose groups at the 24-hour sacrifice. The increase was significant ($p<0.05$) at 325 mg/kg. However, the findings are only suspect and do not provide sufficient evidence to classify RH-287 as clastogenic/aneugenic in this test system. This issue can only be resolved by exposing the test animals to the MTD.

APPENDIX 2

CLOTHIANIDIN (USEPA, 2017): Example For Use Of A Two Generation Reproduction Study For Inhalation Exposure Risk Assessment.

Table 4.5.4a. Summary of Toxicological Doses and Endpoints for Clothianidin for Use in Dietary and Non-Occupational Human Health Risk Assessments.

Exposure/ Scenario	Point of Departure	Uncertainty/ FQPA Safety Factors	Level of Concern (LOC) for Risk Assessment	Study and Toxicological Effects
Acute Dietary Females age 13-49	NOAEL = 25 mg/kg/day	UF_A = 10X UF_H = 10X SF_{FQPA} = 1X	aRfD=0.25 mg/kg/day aPAD=0.25 mg/kg/day	**Rabbit developmental study** LOAEL = 75 mg/kg/day based on increased litter incidence of a missing lobe of the lung
Acute Dietary General population	NOAEL = 25 mg/kg/day	UF_A = 10X UF_H = 10X SF_{FQPA} = 1X	aRfD = 0.25 mg/kg/day aPAD 0.25 mg/kg/day	**Special neurotoxicity/pharmacology study in mice** LOAEL = 50 mg/kg/day based on transient signs of decreased spontaneous motor activity, tremors and deep respirations
Chronic Dietary All populations including infants and children	NOAEL= 9.8 mg/kg/day	UF_A = 10X UF_H = 10X SF_{FQPA} = 1X	cRfD=0.098 mg/kg/day cPAD=0.098 mg/kg/day	**Rat two-generation reproduction study** LOAEL = 31.2 mg/kg/day based on decreased body weight gains and delayed sexual maturation, decreased absolute thymus weights in F1 pups and increased stillbirths in both generations
Incidental Oral (short-term)	NOAEL= 9.8 mg/kg/day	UF_A = 10X UF_H = 10X SF_{FQPA} = 1X	MOE= 100 (residential)	**Rat two-generation reproduction study** LOAEL= 31.2 mg/kg/day based on decreased body weight gains and delayed sexual maturation, decreased absolute thymus weights in F1 pups and increased stillbirths in both generations
Dermal (all durations)	Oral study NOAEL= 9.8 mg/kg/day (dermal absorption = 1% of oral absorption)	UF_A= 10X UF_H= 10X SF_{FQPA}= 1X	MOE= 100 (residential)	**Rat two-generation reproduction study** LOAEL = 31.2 mg/kg/day based on decreased body weight gains and delayed sexual maturation, decreased absolute thymus weights in F1 pups and increased stillbirths in both generations
Inhalation (all durations)	Oral study NOAEL= 9.8 mg/kg/day (inhalation toxicity = oral toxicity)	UF_A = 10X UF_H = 10X SF_{FQPA} = 1X	MOE= 100 (residential)	**Rat two-generation reproduction study** LOAEL = 31.2 mg/kg/day based on decreased body weight gains and delayed sexual maturation, decreased absolute thymus weights in F1 pups and increased stillbirths in both generations
Cancer (oral, dermal, inhalation)	"Not Likely to be Carcinogenic to Humans"			

APPENDIX 2–

CLOTHIANIDIN (USEPA, 2017): Example For Use Of A Two Generation Reproduction Study For Inhalation Exposure Risk Assessment.

Table 4.5.4a. Summary of Toxicological Doses and Endpoints for Clothianidin for Use in Dietary and Non-Occupational Human Health Risk Assessments.

Exposure/ Scenario	Point of Departure	Uncertainty/ FQPA Safety Factors	Level of Concern (LOC) for Risk Assessment	Study and Toxicological Effects
Acute Dietary Females age 13-49	NOAEL = 25 mg/kg/day	UF_A = 10X UF_H = 10X SF_{FQPA} = 1X	aRfD=0.25 mg/kg/day aPAD=0.25 mg/kg/day	**Rabbit developmental study** LOAEL = 75 mg/kg/day based on increased litter incidence of a missing lobe of the lung
Acute Dietary General population	NOAEL = 25 mg/kg/day	UF_A = 10X UF_H = 10X SF_{FQPA} = 1X	aRfD = 0.25 mg/kg/day aPAD 0.25 mg/kg/day	**Special neurotoxicity/pharmacology study in mice** LOAEL = 50 mg/kg/day based on transient signs of decreased spontaneous motor activity, tremors and deep respirations
Chronic Dietary All populations including infants and children	NOAEL= 9.8 mg/kg/day	UF_A = 10X UF_H = 10X SF_{FQPA} = 1X	cRfD=0.098 mg/kg/day cPAD=0.098 mg/kg/day	**Rat two-generation reproduction study** LOAEL = 31.2 mg/kg/day based on decreased body weight gains and delayed sexual maturation, decreased absolute thymus weights in F1 pups and increased stillbirths in both generations
Incidental Oral (short-term)	NOAEL= 9.8 mg/kg/day	UF_A = 10X UF_H = 10X SF_{FQPA} = 1X	MOE= 100 (residential)	**Rat two-generation reproduction study** LOAEL= 31.2 mg/kg/day based on decreased body weight gains and delayed sexual maturation, decreased absolute thymus weights in F1 pups and increased stillbirths in both generations
Dermal (all durations)	Oral study NOAEL= 9.8 mg/kg/day (dermal absorption = 1% of oral absorption)	UF_A= 10X UF_H= 10X SF_{FQPA}= 1X	MOE= 100 (residential)	**Rat two-generation reproduction study** LOAEL = 31.2 mg/kg/day based on decreased body weight gains and delayed sexual maturation, decreased absolute thymus weights in F1 pups and increased stillbirths in both generations
Inhalation (all durations)	Oral study NOAEL= 9.8 mg/kg/day (inhalation toxicity = oral toxicity)	UF_A = 10X UF_H = 10X SF_{FQPA} = 1X	MOE= 100 (residential)	**Rat two-generation reproduction study** LOAEL = 31.2 mg/kg/day based on decreased body weight gains and delayed sexual maturation, decreased absolute thymus weights in F1 pups and increased stillbirths in both generations
Cancer (oral, dermal, inhalation)	"Not Likely to be Carcinogenic to Humans"			

APPENDIX D

A Critique of
US EPA. Hazard Characterization of Isothiazolinones in Support of FIFRA Registration Review (April 6, 2020)

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October 26, 2020

Preamble

The class considered here comprises six pesticidal active ingredients:

- n-butyl-1,2-benzisothiazolin-3-one [BBIT][4299-07-4]
- 1,2-benzisothiazolin-3-one [BIT][2634-22-5]
- 2-n-octyl-4-isothiazolin-3-one [OIT][26530-20-1]
- 4,5-dichloro-2-n-octyl-4-isothiazolin-3-one [DCOIT][64359-81-5]
- 2-methyl-4-isothiazoline-3-one [MIT] [2682-20-4]
- 5-chloro-2-methyl-4-isothiazoline-3-one [CMIT][26172-55-4]

The products containing these chemicals do not bear pesticide labels, and therefore do not communicate potential skin sensitization hazards to consumers. As a consequence, the Environmental Protection Agency (EPA) has used a quantitative approach to assess the skin sensitization potential of the isothiazolinones by identifying induction and/or elicitation skin sensitization thresholds for each chemical. These threshold values are then to be used to characterize risk from skin exposure.

The 6 isothiazolinones were evaluated together as it was recognized that they have common structural characteristics and toxicological properties.

What follows is a critical evaluation of the approach taken by the EPA.

The focus here is on animal and non-animal (*in vitro*) methods for skin sensitization hazard characterization. The value of Human Repeat Insult Patch Test (HRIPT) data is discussed elsewhere.

ANIMAL AND NON-ANIMAL METHODS FOR SKIN SENSITIZATION HAZARD CHARACTERIZATION

1. Introduction

The US EPA. Hazard Characterization of Isothiazolinones in Support of FIFRA Registration Review, prepared in collaboration with the National Toxicology Program's Interagency Coordinating Committee for the Evaluation of Alternative Toxicological Methods (EPA/NICEATM report) makes it plain in the Introduction (page 7) that no additional toxicology

studies were required for evaluation of the isothiazolinone biocides. In addition, the Report indicates that the evaluation has used data generated from *in vitro* and *in chemico* assays. It is surprising that no mention is made of the Local Lymph Node Assay (LLNA). Although this is an *in vivo* assay, there are relevant data available that address the skin sensitizing potency of isothiazolinones, and that could have contributed significantly to these evaluations. No new LLNA studies would have needed to be commissioned. The availability of relevant LLNA data for isothiazolinones (other than BBIT) is mentioned later in the Report (page 9), with an acknowledgement that these assays were performed for the purposes of '*quantitative assessment of skin sensitization potential'.*

2. Alternative methods for the identification of skin sensitizing potential

The EPA/NICEATM report acknowledges that none of the validated non-animal methods that has been assigned OECD test guideline status are currently accepted as stand-alone methods for the purposes of hazard identification (pages 11 and 12). A summary of these tests and how they align with Key Events (KE) of the Adverse Outcome Pathway (AOP) for skin sensitization is provided in Appendix 1. The point should also be made that none of these assays has been validated for the purposes of measuring skin sensitizing potency (OECD, 2015: 2018a; b).

The EPA/NICEATM report goes on to state that because no individual validated non-animal methods are currently viewed as a stand-alone test for hazard identification, attempts have been made to develop combination strategies (Integrated Approaches to Testing and Assessment [IATA] and Defined Approaches [DA]) that seek to bring together information from various sources to enhance the accuracy with which skin sensitization hazards are identified (page 12). The report describes the differences between IATA and DA (page 12) and summarizes efforts that have been made to evaluate such approaches in terms of both hazard identification and potency assessment (Kleinstreuer et al., 2018) (pages 12 and 13).

3. The Artificial Neural Network (ANN) model

Among the 6 methods considered by Kleinstreuer et al. (2018) was the Artificial Neural Network (ANN) model (page 13 of the EPA/NICEATM report). This was developed by the Japanese company Shiseido in conjunction with the Japanese Cosmetic Industry Association (Hirota et al., 2015), and built on previous studies reported by the same group the previous year (Tsujita-Inoue et al., 2014).

The ANN is described as a non-linear statistical model that combines multiple *in vitro* and *in silico* parameters that are aligned with Key Events 1, 2 and 3 in the AOP for skin sensitization. This method seeks to predict LLNA EC3 values using various combinations of three types of *in vitro* tests: (1) SH protein reactivity test or Direct Peptide Reactivity Assay [DPRA], (2) human Cell Line Activation Test [h-CLAT], and (3) an antioxidant response element [ARE] test or KeratinoSens. Examples of possible ANN configurations are h-CLAT+DPRA+ARE and h-CLAT+SH+ARE.

It is reported that multiple ANN models have been built, with physicochemical properties of the test chemical and Quantitative Structure Activity Relationship (QSAR) predictions included as

descriptors in addition to those deriving from *in vitro* methods. These ANN models are described as consisting of an input layer (comprising descriptors from *in vitro* or *in silico* results (and possibly physicochemical properties), a 'hidden layer', and an output layer (the output being an EC3 value) (Kleinstreuer et al., 2018).

In the analyses reported by Kleinstreuer et al (2018) 2 versions of the ANN model were evaluated (DPRA+h-CLAT and DPRA+h-CLAT+KeratinoSens). DPRA+h-CLAT showed 61.1% accuracy for measuring relative potency in the context of 3 potency classes, and 65.1% accuracy for 3 potency classes based on LLNA data, The second version, DPRA+h-CLAT+KeratinoSens, was found to be 62.7% accurate for 3 potency classes, and 69.8% accurate for 3 potency classes based on LLNA data. The LLNA was reported to be 59% accurate.

The EPA/NICEATM report states that of the 6 approaches evaluated by Kleinstreuer et al (2018) '*the artificial neural network (ANN) model* ..was *...unique in its ability to estimate LLNA EC3 values* (page 13). As will be illustrated below, the data generated with the isothiazolinones appear not to support this view.

The Report goes on to state that the EPA determined that the *in vitro* and *in silico* studies provide information that is more reliable, reproducible and human-relevant than the LLNA, and that, as a consequence results of the ANN-EC3 DA were used to derive EC3 values to extrapolate dermal risk for currently registered isothiazolinones as part of a registration review (page 13).

4. ANN results with isothiazolinones

It is instructive to compare results generated using ANN models with those derived from LLNA studies. This is, of course, relevant because the stated aim of the ANN approach was to develop a system to replace the LLNA (Hirota et al., 2015).

Apparently data from 3 isothiazolinones (CMIT/MIT, MIT and BIT) were employed in the development of ANN models. However, as described in supplementary data from Hirota et al (2005), only CMIT/MIT was used in the full h-CLAT+DPRA+ARE and h-CLAT+SH+ARE ANN models due to the lack of availability of ARE and SH assay data for both MIT and BIT. Data for CMIT/MIT, MIT and BIT are available from the simpler h-CLAT+DPRA model. The % EC3 values predicted for CMIT/MIT, MIT and BIT in the ANN models are compared with LLNA EC3 values (Table 1).

Table 1:
EC3 values (%) measured in the LLNA and estimated from three ANN models[a]

Chemical	*LLNA*	*ANN models*		
		h-CLAT+DPRA	*h-CLAT+DPRA+ARE*	*h-CLAT+SH+ARE*
CMIT/MIT	*0.005*	*0.13*	*0.10*	*0.07*
MIT	*1.9*	*0.70*	*-*	*-*
BIT	*2.3*	*0.03*	*-*	*-*

[a] *Hirota et al (2015)*

It is clear from the data in Table 1 that there are very significant differences between LLNA EC3 values and EC3 values estimated from the ANN models. The EC3 value for CMIT/MIT is substantially higher than the LLNA EC3 value in the h-CLAT+DPRA model (by a factor of 26), in the h-CLAT+DPRA+ARE model (by a factor of 20), and in the h-CLAT+SH+ARE model (by a factor of 14). In contrast, the predicted EC3 values for MIT and BIT in the h-CLAT+DPRA model are lower, and in the case of BIT very substantially lower, than the relative LLNA EC3 vales. Thus, the EC3 value for MIT in the h-CLAT+DPRA model was a factor of 2.7 lower than the LLNA EC3 value, and the EC3 value for BIT in the h-CLAT+DPRA model was a factor of 76.7 lower than the LLNA EC3 value (Table 1).

In the EPA/NICEATM Report two ANN models were evaluated: h-CLAT+DPRA and h-CLAT+DPRA+ARE (in this case the ARE used was KeratinoSens) (page 17). The data are summarized below in Table 2 where all EC3 values are recorded as % values. In this Table ANN results obtained with BBIT have been excluded because there are no LLNA data available for this chemical with which comparisons can be drawn. Two sources of LLNA data are displayed in Table 2.

The first are LLNA data derived from studies reported by Dow/DuPont. A total of 17 LLNA studies were provided comprising between 2 and 4 individual studies for each of the 5 isothiazolinones considered. A representative EC3 for each chemical was selected from assays that had employed either acetone or acetone:olive oil as the vehicle. Two EC3 values were provided for OIT as there were two eligible studies for this chemical (EPA/NICEATM report, page 14).
The second set of LLNA (labelled USEPA in Table 2) originally incorporated the 17 studies reported by Dow/DuPont, together with another 15 studies derived from the scientific literature. Together there were a total of 32 studies available, with between 3 and 13 being available for each of the chemicals listed. Following elimination of studies that did not meet selection criteria, a single representative mean EC3 value was calculated for each isothiazolinone.

The data summarized in Table 2 are not dissimilar to those in Table 1. It is instructive to again examine the differences between measured EC3 values (LLNA data) and predicted EC3 values (ANN data) for each of the 5 isothiazolinones listed. For ease of comparison the mean of the Dow/DuPont and USEPA data are used for the purposes of comparison with the ANN models.
[In addition, see Appendix 2 which summarizes another analysis of available LLNA EC3 data provided by Dow/DuPont for DCOIT, CMIT/MIT, OIT, MIT and BIT].

Table 2**:**
EC3 values (%) measured in two separate LLNA assessments, and EC3 values (%) and predicted by two ANN models. Data for BBIT omitted because no LLNA data were presented

IT	*LLNA(1) (Dow/DuPont)*	*LLNA(2) (USEPA)*	*ANN models* [a]	
			h-CLAT+DPRA	*h-CLAT+DPRA+ARE*
DCOIT	*0.004*	*0.008*	*0.0566*	*0.023*
CMIT/MIT	*0.002*	*0.018*	*0.121*	*0.492*
OIT [b]	*0.225*[b]	*0.361*	*0.0569*	*0.015*

MIT	*0.863*	*1.154*	*1.775*	*0.826*
BIT	*1.54*	*10.57*	*0.934*	*0.341*

[a] *Hirota et al (2005)*
[b] *Average of 2 values (0.20 and 0.25)*

(a) DCOIT: a mean EC3 value of 0.006% can be used for the Dow/DuPont and USEPA LLNA EC3 data. This figure is 9.4-fold lower than the EC3 predicted by the ANN h-CLAT+DPRA model, and 3.83-fold lower than that predicted by the ANN h-CLAT+DPRA+ARE model.

(b) CMIT/MIT: here a mean value of 0.01% can be used for the Dow/DuPont and USEPA LLNA EC3 data This is substantially lower than the EC3 values predicted by the ANN models. Thus, the mean LLNA EC3 value is 12.1-fold lower than the EC3 value predicted using the ANN h-CLAT+DPRA model, and 49.2-fold lower than the EC3 value predicted using the ANN h-CLAT+DPRA+ARE model.

(c) OIT: in this case a mean value of 0.293% is used for the Dow/DuPont and USEPA LLNA EC3 data. This is some 5.2-fold higher than the EC3 value predicted by the ANN h-CLAT+DPRA model, and 19.5-fold higher than the EC3 value predicted by the ANN h-CLAT+DPRA+ARE model.

(d) MIT: here a mean value of 1.01% is used for the Dow/DuPont and USEPA LLNA data. This is 1.75-fold lower than the EC3 value predicted by the ANN h-CLAT+DPRA model, and 1.12-fold higher than the EC3 value predicted by the ANN h-CLAT+DPRA+ARE model.

(e) BIT: a mean value of 6.06% is used here for the Dow/DuPont and USEPA LLNA data. This is 6.4-fold higher than the EC3 value predicted by the ANN h-CLAT+DPRA model, and 17.8-fold higher than the EC3 value predicted by the ANN h-CLAT+DPRA+ARE model.

Taken together it is possible to make some observations from the data summarized in Tables 1 and 2. In general terms it can be concluded that:

- with **CMIT/MIT** EC3 values measured in the LLNA were **substantially lower** than EC3 values predicted using ANN models
- with **MIT** EC3 values measured in the LLNA were **2-3-fold higher or lower** than EC3 values predicted using ANN models.
- with **BIT** EC3 values measured in the LLNA were **substantially higher** than EC3 values predicted using ANN models.
- with **DCOIT** EC3 values measured in the LLNA were **lower/substantially lower** than EC3 values predicted using ANN models.
- with **OIT** EC3 values measured in the LLNA were **higher or substantially higher** than EC3 values predicted using ANN models.

On this basis it can be concluded that, compared with EC3 measurements made using the LLNA, the ANN models under-predict the potency of CMIT/MIT and DCOIT, and over-predict the potency of BIT and OIT. Although there are differences, the EC3 values for MIT from the LLNA and ANN models are broadly comparable.

There are marked differences in EC3 values measured by the 2 approaches that should raise considerable concerns. However, the EPA/NICEATM report states the following (page 16):

'The quantitative EC3 predictions derived from the ANN DAs were similar to the LLNA EC3 values, with overlapping 95% confidence intervals in most cases, with the exception of CMIT/MIT, where the upper bound of the in vivo CI was 3.5-fold less than the lower bound of the in silico CI'

However, it must be borne in mind that the confidence intervals (as recorded in Table 5, page 17 of the EPA/NICETAM Report) were substantial.

Considerations and the conclusions drawn are as follows:

(a) There are, in many instances, very substantial differences between EC3 values measured in the LLNA and EC3 values predicted using ANN models.

(b) Moreover, the differences between LLNA EC3 values and ANN predicted EC3 values are inconsistent, (and as a result the rank order of potency among the isothiazolinones would be different).

(c) It is likely that these differences are attributable to the fact that isothiazolinones lie outside the applicability domain of the ANN models.

(d) With respect to point (c) above, it is also worth noting that – in common with other *in vitro* methods – chemicals that are poorly water soluble will likely fall outside the applicability domain of ANN models (Kleinstreuer et al., 2018). This will be of relevance when considering the isothiazolinones, and in particular DCOIT and OIT which are both poorly water soluble.

(e) Data are lacking on the vehicles that we used for assessment of the isothiazolinones using the ANN, and it is possible that if different vehicles were employed that could have impacted on the predicted EC3 values

(f) At this time ANN models cannot be considered to provide an accurate indication of skin sensitizing potency, and it would be inappropriate to use EC3 values predicted by ANN models in assessment of skin sensitization risks posed by exposure to isothiazolinones.

5. Reflections on the LLNA and ANN models

It is important to preface this section by emphasizing that the authors of this critique do not hold a brief for promotion of the LLNA. They are both committed to animal welfare, and to the development of non-animal methods in toxicology. However, it is important that this commitment is tempered by realism and an acknowledgement that such new methods must at least maintain, or better still improve, the ability of toxicologists to identify and characterize hazards and develop accurate assessments of health and environmental risks. Moreover, when there are available reliable *in vivo* data for assessing potency and risk (as is the case here) it should be included for consideration alongside any new data that have been generated.

There is a need, therefore, that new approaches are evaluated carefully and dispassionately. It is in that spirit that the authors would like to reflect on the data summarized above and the comparisons drawn between the LLNA and ANN models. In this case perhaps the key consideration is the question of relevance.

The EPA/NICEATM report correctly draws attention to the fact that establishing scientific confidence in new methods has two major components: *relevance* and *reliability* (page 19). This is, of course, true. It is important, however, to consider how these features are measured and established, and here we concentrate on *relevance.* One example taken from the EPA/NICEATM report provides an illustrative example. In the text on page 19 the following statement is made:

'The h-CLAT is a cell-based assay that identifies skin sensitizers by examining changes in the expression of cell surface markers (CD54 and CD86) implicated in dendritic cell activation, the third key event of the skin sensitization AOP. Following exposure of the THP-1 human monocyte cell line to the test substance expression levels of CD54 and CD86 are quantified by flow cytometry and compared to controls. Thus (KeratinoSens) and h-CLAT are considered more human relevant and mechanistically driven compared to the LLNA which uses the mouse and models an apical outcome'.

In considering this assertion it must be appreciated that the acquisition of skin sensitization is an extremely complex biological process that involves multiple cellular and molecular interactions that are tightly regulated in time and space. The roles played by dendritic cells (both epidermal Langerhans cells and dermal dendritic cell sub-populations) are exceedingly complex, and collectively these cells are responsible for the recognition, internalization, processing, transport and eventual presentation of chemical-protein adducts to responsive T lymphocytes. These functions of dendritic cells require receipt of the appropriate signals, activation, changes in phenotype and relocation to different anatomical sites (Cumberbatch et al., 2003, Ainscough et al., 2013; Clausen and Stoitzner, 2015; Deckers et al., 2017).

Given the diversity of cutaneous dendritic cells, and the complexity of their roles in the acquisition of skin sensitization, it is remarkable that the h-CLAT method, that relies solely on measurement of the up-regulation of membrane CD54 and/or CD86 works as well as it does. However, it is perhaps not surprising that the method has limitations and is not seen as being appropriate for use as a stand-alone assay for hazard identification.

The question is whether addition of a test chemical to cells (albeit human cells) in culture and measuring changes in the expression of just 2 membrane activation markers is more or less *relevant* than the LLNA that incorporates as it does the complexity of dendritic cell biology in the appropriate 3-dimensional anatomical and physiologic matrices that is required for the successful acquisition of skin sensitization.

In this context it is relevant to consider briefly the alignment of *in vitro* test methods with the AOP. In the statement quoted above from page 19 of the EPA/NICEATM report reference is made to the fact that h-CLAT measures changes that are implicated in the third key event of the skin sensitization AOP. This is true. However, it is important to recall that an AOP – which can be usefully defined as 'analytical constructs that describe series of linked events (key events) that

culminate in an adverse health effect' – does more than provide a template for the identification of likely read-outs for novel predictive test methods. The AOP in fact reflects those pivotal cellular and molecular interactions that must occur in sequence or in parallel for an adverse health effect to be induced. In effect the AOP breaks down into component parts the critical events that occur during the manifestation of a toxic reaction *in vivo*. With this in mind it is important to appreciate that it is not just *in vitro* methods that are aligned with the AOP for skin sensitization. The LLNA in fact can be seen as a synthesis of all the key events of the pathway. For a lymphocyte proliferative response to be provoked in a draining lymph node – the read-out of the LLNA - it is necessary that the test chemical encountered on the skin gains access to the viable epidermis via the stratum corneum and forms appropriate stable conjugates with host proteins (KE1). It is necessary also that the chemical interacts with epidermal cells to elicit signals (danger signals) that activate the innate immune system (KE2). Among the changes induced is the activation, functional differentiation and mobilization of various populations of dendritic cells (KE3). Activated dendritic cells then migrate to regional lymph nodes where they present antigen to responsive T lymphocytes that are induced to divide and differentiate (KE4), at which point skin sensitization is acquired.

So the LLNA does, in fact, incorporate – by necessity - **all** of the key events that comprise the AOP for skin sensitization. It is, therefore misleading for the EPA/NICEATM report (on page 19) to describe h-CLAT for instance as being: *'more human relevant and mechanistically driven, compared to the LLNA which uses the mouse and models an apical outcome'*. If one defines an apical outcome as being an observable outcome in a whole organism that reflects a toxic change, then the LLNA does have an apical endpoint – but an endpoint that is entirely dependent upon all of the key events taking place following exposure to the test chemical, and that lead collectively to the acquisition of skin sensitization.

These are important points to bear in mind when considering the relevance and reliability of test methods that are going to be employed for hazard characterization and the assessment of skin sensitization risks that can affect the health of exposed subjects.

6. Other considerations and concluding comments

- It is understood that there may be no appetite for commissioning new LLNA studies, but (with the exception of BBIT) there are already available LLNA data and LLNA EC3 values for the isothiazolinones that could usefully inform potency assessment and hazard characterization.
- If the LLNA is inadequate for the accurate assessment of skin sensitizing hazards why has a model been selected (ANN) that seeks to predict LLNA EC3 values.
- It is important to appreciate that the ANN system has not been widely adopted or formally validated.
- It is a mistake to believe that a composite model such as the ANN system is itself validated simply because some of the individual test methods it incorporates have themselves been validated (for hazard identification).
- With respect to the ANN system, it would appear that incorporating experience from a wider range of chemistries will be required before the model can be used with confidence for hazard characterization and risk assessment

- There are many versions of the ANN system that include in their configuration different non-animal endpoints, using different test methodologies, and which may or may not incorporate physicochemical and QSAR data. It is not clear that there is any consensus regarding the most accurate ANN model, or how version control is managed.
- The EC3 values for isothiazolinones predicted using the ANN models are in many instances very different from EC3 values measured using the LLNA. No consistent relationships with LLNA data are observed. These differences would have a substantial impact on how skin sensitizing hazards are characterized for this class of chemicals. There is no rationale for why the EC3 values are so different, but the most likely explanation is that the isothiazolinones are outside the current applicability domain of the ANN models
- It would be inappropriate at this time to use EC3 values predicted by ANN models for the purpose of hazard characterization or risk assessment.
- Available LLNA, combined of course with relevant human data, would provide a more certain and more secure approach to hazard characterization of the isothiazolinones.

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Appendix 1

A summary of validated non-animal tests for skin sensitization hazard identification that have been assigned OECD Test Guideline status (as of September 2020)

Methods are here aligned with the Adverse Outcome Pathway (AOP) Key Event (KE) that they seek to reflect

KE1: *In chemico* skin sensitisation assays addressing the AOP key event on covalent binding to proteins (OECD TG 442C): Direct Peptide Reactivity Assay (DPRA) and Amino acid Derivative Reactivity Assay (ADRA)(OECD 442C). These tests seek to measure the electrophilic activity of test chemicals.

KE2: *In vitro* skin sensitisation assays addressing the AOP key event on keratinocyte activation (OECD TG 442D): ARE-Nrf2 Luciferase test methods: Keratinosens, and LuSens (OECD 442D). In common with the DPRA, this approach is based upon measurement of the electrophilic activity of sensitising chemicals.

KE3: *In vitro* skin sensitisation assays addressing the key event on activation of dendritic cells on the adverse outcome pathway (OECD TG 442E): human Cell Line Activation Test (h-CLAT), Myeloid U937 Skin Sensitisation test (U-SENS), and IL-8 Luc assay (OECD 442E). The h-CLAT measures the ability of test chemicals to induce the up-regulated expression of activation markers (CD54 and/or CD86) by a cultured human monocytic leukaemia cell line (THP-1) as a surrogate for DC. The U-SENS method is similar to h-CLAT but employs instead a histiocytic lymphoma cell line, U937 to measure induced changes in the expression of CD86. The third method, the IL-8 Luc assay, measures induced changes in the expression of the cytokine IL-8 by a THP-1 cell line expressing a reporter gene.

Appendix 2

A summary of LLNA EC3 values derived from another analysis conducted by Dow/DuPont of available data for isothiazolinones: DCOIT, CMIT/MIT, OIT, MIT and BIT LLNA 3): a comparison with the LLNA EC3 data from Dow/DuPont (LLNA 1) and USEPA (LLNA 2) recorded in Table 2 in the main boy of this report

IT	*LLNA(1) (Dow/DuPont)*	*LLNA(2) (USEPA)*	*Dow/DuPont LLNA(3)*
DCOIT	*0.004*	*0.008*	*0.0076*
CMIT/MIT	*0.002*	*0.018*	*0.0076*
OIT [b]	*0.225*[b]	*0.361*	*0.29*
MIT	*0.863*	*1.154*	*1.38*
BIT	*1.54*	*10.57*	*2.3*

The EC3 values that derive from the DuPont LLNA studies represent median values (other than for DCOIT) from studies conducted with DCOIT (n=2), CMIT/MIT (n=10), OIT (n=4), MIT (n=4) and BIT (n=7).

It is clear that the analyses of available data conducted independently by DuPont yield EC3 values that are very similar to those shown in Table 2, and which derive from Dow and the USEPA/NICEATM report.