Independent Lubricant Manufacturers Association

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February 23, 2018

Via Electronic Mail

Ms. Michelle Ramirez
Environmental Scientist
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency
1001 I Street
Sacramento, California 95814

Re: OEHHA's Notice of Intent to List: TRIM® VX - Proposition 65

Dear Ms. Ramirez:

The Independent Lubricant Manufacturers Association ("ILMA" or "Association") submits the following comments, opposing the California Environmental Protection Agency, Office of Environmental Health Hazard Assessment's ("OEHHA") Notice of Intent to list the discontinued product TRIM® VX pursuant to the "Safe Drinking Water and Toxic Enforcement Act of 1986" – commonly referred to as Proposition 65 ("Prop 65"), as a chemical known to the State of California to cause cancer.

OEHHA's proposed listing pursuant to the Authoritative Bodies listing mechanism is based on the National Toxicology Program's[1] ("NTP") conclusions contained in its Final Technical Report for its two-year inhalation study of TRIM® VX. ILMA commented extensively in written submissions to NTP on its Draft and Final Technical Report and made oral presentations during the Peer Review Panel that reviewed the draft conclusions. The Association expressed concerns with the manner in which the NTP study was conducted and the conclusions reached.

As a result, the Association objects to OEHHA predicating its Prop 65 listing on NTP's study and respectfully requests that OEHHA withdraw its Notice of Intent to List TRIM® VX.

[1] The National Toxicology Program is one of several institutions designated as authoritative for the identification of chemicals as causing cancer Title 27, California Code of Regulations - Section 25306 (m).

Introduction to ILMA

ILMA is a national trade association with 350 member companies that is headquartered in Alexandria, Virginia. ILMA's manufacturing members blend, compound, and sell over 25 percent of the United States' lubricant needs (*e.g.*, passenger car motor oils, gear oils, and hydraulic fluids) and over 75 percent of the metalworking fluids ("MWFs") utilized in the country. The overwhelming majority of ILMA's manufacturing members are "small businesses" based on the Small Business Administration's size standards. ILMA members, as manufacturers, are classified at NAICS 324191.

Independent lubricant manufacturers are neither owned nor controlled by the companies that explore for or refine crude oil to produce lubricant base stocks or that produce chemical additives. Base oils are purchased from refiners and re-refiners, who are also direct competitors in the sale of finished products. Additives are purchased from suppliers, who also may be direct competitors in the sale of finished products. ILMA members succeed over their suppliers/competitors by manufacturing and distributing high-quality, often specialized, lubricants accompanied by localized, allied services to their customers.

Lubricants are essential to the U.S. economy. Americans cannot get to work without the engine oils, transmission fluids and other automotive lubricants in their vehicles. Manufacturers cannot operate most of their machinery without industrial oils and hydraulic fluids. MWFs are used to bend, shape or cut metal for the production or fabrication of automobiles, military equipment, airplanes, medical devices and thousands of other products. ILMA members' products are vital to the economic freedom and prosperity enjoyed by the U.S.

NTP Conducted a Problematic Study

ILMA submitted detailed comments to NTP on its initial Draft Technical Report[2] and Final Technical Report.[3] Without re-litigating the entire NTP review process, it is important to highlight salient shortcomings with the NTP's study and the resulting conclusions.

The material used for the study was far beyond the manufacturer's recommended shelf life. Despite the clear statement that the product had a recommended shelf life of 12 months, NTP began its study on a fluid that was already eight months old and, therefore, many of the results came from an old, separated, and likely chemically altered version of TRIM® VX. Although not stated in the report, the age of each lot of TRIM® VX was approximately seven to eight months at the start of the respective studies. In 2005, ILMA sent a letter to Dr. Morgan at NIEHS, stating that the recommended shelf life for MWFs was 12 months. Given that the samples of TRIM® VX became substantially older than 12 months during the course of the NTP studies, age-related separation and chemical alteration of the TRIM® VX could be expected. A number of compounds that were in the product as formulated were not found in the NTP analysis and a number of measured components that were in the VX formula were reported at concentrations significantly different from the VX formula, possibly indicating degradation.

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[2] *See* ILMA letter to Dr. Yun Xie – NTP Designated Federal Official (February 6, 2016).
[3] *See* ILMA letter to Dr. Yun Xie – NTP Designated Federal Official (December 13, 2016).

NTP did not provide an adequate explanation within the two-year study to address the issues of degradation and separation. Master Chemical advised its customers that the product had a 12-month maximum shelf life; however, the samples that NTP utilized in the study were 30.5 months old at the conclusion. MWFs are unique formulations and the different components that comprise the mixture interact so differently that each product has a distinct lifespan. In an effort to ensure that NTP firmly understood the lifecycle of TRIM® VX, ILMA provided the information well in advance of the commencement of the study. NTP was put on notice of the product's life span, and, despite that information, NTP elected to proceed with the study on a product significantly beyond its useful shelf life.

The NTP Peer Review Panel also expressed serious reservations about the sample and its treatment:

> In addition, the lack of data presented regarding bacterial and fungal growth is particularly concerning. During the course of the [Peer Review] Panel discussion, there was much confusion about product testing in an attempt to clarify that the TRIM® VX samples did not become contaminated during the course of the study. The following exchange during the Panel meeting is particularly illuminating of this concern (Recording Segment #59 – Time Marker 20:58):
>
> **Dr. Brock:** So, in other words, you did the stability real-time with the unfrozen material by comparing it to the frozen sample? Do I understand that correctly?
>
> **Dr. Ryan:** Yes. So when we receive the test material at the time of receipt we take aliquots out and freeze them, so we can compare our data of all the test material throughout the study. And then we can compare the data currently compared to the reference sample so we have an understanding if there was any degradation over time.
>
> **Dr. Brock:** And it assumes that frozen samples over time don't degrade as well?
>
> **Dr. Ryan:** That is correct.
>
> **Dr. Brock:** And did they? [SEP]
>
> **Dr. Ryan:** I believe they were stored at appropriate conditions.
>
> **Dr. Brock:** Appropriate conditions. But did they degrade over time?

This statement is immensely problematic. MWFs are complex mixtures and must be stored carefully. These emulsions break down quickly under inappropriate storage conditions and causes the product to degrade and separate exponentially faster compared to when the product is stored properly. In essence, NTP's "test sample" or the control that served as the basis for comparison to ensure that the material was not degrading and separating was itself very likely degraded and separated. Neither the "Materials and Methods" section nor the "Chemical Characterization and Generation of Chamber Concentration" section adequately addressed the concerns ILMA raised multiple times. This is highly disappointing and further calls into question NTP's conclusions.

Beyond the issues with the storage of the product, NTP erroneously selected an inappropriate dose level. The choice was not predicated upon sound science or a legitimate justification, but rather was chosen for ease of comparison to a prior NTP study. This is problematic and further calls into question the conclusions from the final report.

The highest dose level of 100 mg/m^3 selected for two-year study was too high because fibrosis was seen in both male and female rats and mice at that level in the 90-day study; 50 mg/m^3 would have been the more appropriate choice. Further, NTP's draft report notes on page 55 that "[t]he highest exposure concentration was based on the incidence and severity of lung fibrosis in the current 3-month study. Although minimal lung fibrosis was present in rats exposed to 50 and 100 mg/m^3, this lesion was not expected to affect survival in the two-year study, and use of the same exposure concentrations for rats and mice would facilitate inter-species comparisons. In addition, *these concentrations were used in the two-year study of CIMSTAR® 3800 in Wistar Han rats, which allows for comparisons between the two metalworking fluid studies."*

The increased incidence of tumors in mice only at 100 mg/m^3, the equivocal evidence of tumors in rats only at 100 mg/m^3, the absence of trends for increased tumors at lower doses, the lack of positive results in genotoxicity screening assays of both TRIM® VX or some of its components, the lack of systemic tumors or toxicity, and the presence of significant non-neoplastic lesions in the respiratory tract (including fibrosis) collectively suggest a possible non-genotoxic mechanism for production of the observed tumors.

Dr. Brock also questioned the selection of 100 mg/m^3 dose level during his comments at the Panel meeting (Recording Segment #61 – Time Market 11:41):

> **Dr. Brock:** For the study design, the dose levels used for the two-year bioassay in rats and mice were 10, 30, and a 100 mg/m^3 and this is the result of the three- month chronic studies . . . Specifically the authors state that the high dose for the two-year studies was based on the occurrence of lung fibrosis in both species.
>
> The incidences of severity of fibrosis at 50 and 100 mgs per cubic meter in rats and mice in the subchronic studies were essentially the same. Moreover, pathological findings at 50 and 100 mgs per cubic meter in rats and mice in the subchronic findings were quite similar. ***Therefore, it is the opinion of this reviewer that the high dose in the two-year studies were too high and an exposure concentration of 50 milligrams per cubic meter would have been sufficient for these studies. Unfortunately this cannot be corrected.*** [Emphasis added].
>
> It is recommended, however, that the authors further describe in the discussion section dose selection based on the totality of the three-month data and the relevance of findings in the tox studies – this is weirdly written – relative to the doses used in the two-year study.
>
> Ostensibly what I'm saying here is I think the dose levels were too high, particularly at the high dose, given the occurrence of fibrosis across all the doses in the three-month study. So you would expect some sort of fibrosis in the two- year study and of course you a get a carcinogenic outcome. I think that has to be discussed relative to dose level selection in greater detail than what's occurring in the report.

> More troubling was the response to Dr. Brock's comments below (Recording Segment #61 – Time Marker 25:20):
>
> **Dr. Ryan:** In addition -- we don't mention this -- these inhalation studies are quite large, and logistically it's helpful for us to have similar exposure concentrations. And as I already mentioned in the report, we also aimed to be able to do a comparison to CIMSTAR® 3800, which had these similar dose selections. So even though, you know, we did, you know, aim to look at all the data within three-month studies, we did focus in on those factors. And we can add more clarity.
>
> **Dr. Brock:** Yeah. I can appreciate the complexity of two-year inhalation bioassays since I've done several of them. ***And to use the same concentrations for rats and mice because it's easier is not a good answer, you know*** [emphasis added]. I know NTP has used multiple -- different doses for different, for both species within the same study paradigms. So it still gets back to the concept of a much more robust dose justification and ultimately explaining the data for its carcinogenic outcome in the discussion section, relative to the dose levels that were selected.

NTP attempts to provide additional justification for its selection of the highest dose level, but Dr. Ryan's commentary during the Panel meeting was illuminating and seems to be the controlling justification for the concentrations selected. To reiterate Dr. Brock's point, "to use the same concentrations because it is easier . . . is not a good answer."

Further, the high aerosol concentrations were not representative of occupational exposures as highlighted below as ILMA originally addressed in its February 2 letter to NTP.

> ILMA recommended that concentrates of soluble oil be diluted with water (1:20) before use in studies with laboratory animals. The reason, as stated by ILMA, is that "any change in product chemistry (including the possible reaction of water with other chemical components in the product concentrate) that might occur upon dilution would not occur if the soluble oil product concentrate were to be directly aspirated." While the use of undiluted concentrate had a definite advantage in terms of generating an aerosol without excessive humidity, the lack of dilution with water again raises a question of how representative the laboratory aerosol was of aerosols of this MWF in the workplace.
>
> Indeed, NTP acknowledges that the aerosols generated for the study were done so for the sake of ease and are not representative of potential workplace exposures:
>
> Because it is technically difficult to generate and expose animals to liquid aerosols containing high water content, the metalworking fluid aerosols in the NTP studies were generated from undiluted concentrates and diluted with clean air to produce the desired concentrations. Thus, the exposure concentrations used in these studies were ***considerably higher*** than those encountered in an occupational setting."[Emphasis added.]

The issues outlined call into question the manner in which NTP conducted its study and the relevance of its conclusions.

Issues with NTP's Study Preclude OEHHA from Listing TRIM® VX Via the Authoritative Bodies Listing Mechanism

OEHHA has established clear, objective criteria for utilization of its Authoritative Bodies mechanism to list chemicals on Prop 65. As noted in the rules, "[A]fter an authoritative body has made a determination about a chemical, OEHHA evaluates whether listing under Proposition 65 is required using the criteria contained in the regulations." A chemical must be listed under the Prop 65 regulations when two conditions are met:

1. An authoritative body formally identifies the chemical as causing cancer (Section 25306(d)); and,
2. The evidence considered by the authoritative body meets the sufficiency criteria contained in the regulations (Section 25306(e)).

As such, the NTP study must fulfill those criteria before TRIM® VX can be properly listed on Prop 65 in accordance with the Authoritative Bodies listing procedure.

Looking first at Title 27, California Code of Regulations, Section 25306 (d), the regulations state:

> (d) For purposes of this section a chemical is "formally identified" by an authoritative body when the lead agency determines that:
>
> (1) the chemical has been included on a list of chemicals causing cancer or reproductive toxicity issued by the authoritative body; or is the subject of a report which is published by the authoritative body and which concludes that the chemical causes cancer or reproductive toxicity; or has otherwise been identified as causing cancer or reproductive toxicity by the authoritative body in a document that indicates that such identification is a final action; and
>
> (2) the list, report, or document specifically and accurately identifies the chemical, and has been:
>
> > (A) Reviewed by an advisory committee in a public meeting, if a public meeting is required, or
> >
> > (B) Made subject to public review and comment prior to its issuance, or
> >
> > (C) Published by the authoritative body in a publication, such as, but not limited to, the federal register for an authoritative body which is a federal agency, or
> >
> > (D) Signed, where required, by the chief administrative officer of the authoritative body or a designee, or
> >
> > (E) Adopted as a final rule by the authoritative body, or
> >
> > (F) Otherwise set forth in an official document utilized by the authoritative body for regulatory purposes.

Further, Title 27, California Code of Regulations, Section 25306 (e) mandates:

> (e) For purposes of this section, "as causing cancer" means that either of the following criteria has been satisfied:
>
> > (1) Sufficient evidence of carcinogenicity exists from studies in humans. For purposes of this paragraph, "sufficient evidence" means studies in humans indicate that there is a causal relationship between the chemical and cancer.
> >
> > (2) Sufficient evidence of carcinogenicity exists from studies in experimental animals. For purposes of this paragraph, "sufficient evidence" means studies in experimental animals indicate that there is an increased incidence of malignant tumors or combined malignant and benign tumors in multiple species or strains, in multiple experiments (e.g., with different routes of administration or using different dose levels), or, to an unusual degree, in a single experiment with regard to high incidence, site or type of tumor, or age at onset.

As detailed above, the NTP study was faulty for several reasons. The sample used was well beyond its recommended "shelf life," and it was stored under inappropriate conditions. An aerosol was then generated using a product that was likely degraded and separated and not representative of TRIM® VX. Further, NTP's dose level of 100 mg/m^3 was inappropriately selected. To reiterate the NTP peer review panel member, "The highest dose level of 100 mg/m^3 selected for two-year study was too high because fibrosis was seen in both male and female rats and mice at that level in the 90-day study; 50 mg/m^3 would have been the more appropriate choice."

Most importantly, Title 27, California Code of Regulations Section 25306 (f) clearly states, "the lead agency shall find that a chemical does not satisfy the definition of "as causing cancer" if scientifically valid data which were not considered by the authoritative body clearly establish that the chemical does not satisfy the criteria of section (e). . ."

From ILMA's perspective, the NTP's election to choose a dose level of 100 mg/m^3 when the 50 mg/m^3 would have provided an appropriate level is tantamount to disregarding scientifically valid data. That issue is compounded by the fact that the materials used to generate the aerosol for that level was from a non-representative, degraded, and inappropriately stored sample. Simply stated, the NTP study fails to meet to the objective criteria OEHHA uses to list chemicals under its Authoritative Bodies listing mechanism. Therefore, listing TRIM® VX on Prop 65 is both inappropriate and counter to California's regulatory requirements.

Metalworking Fluids are Inherently Unique

If OEHHA proceeds with its Prop 65 listing for the discontinued product TRIM® VX, it must carefully articulate that it is only listing that product. What makes individual MWF mixtures unique and work well in a specific, end-use application are significant variations in the formulations. As a result, these formulations are closely guarded trade secrets and its component

ingredients differ considerably. Simply put, the results of the NTP's study, as problematic as they are, are limited only and exclusively to the now-discontinued product, TRIM® VX.[4]

In its February 2 comment letter to NTP, ILMA noted that the bridging principles outlined in the Occupational Safety and Health Administration's ("OSHA") Hazard Communication Standard 2012 do not allow for extrapolation of the results from this study to be applied to other MWFs:

> NTP is aware that MWFs are complex mixtures, that the substances in MWFs vary considerably and that thousands of formulations are commercially available.
>
> Indeed, it was just these circumstances that resulted in NTP and NIOSH collaborating on a selection process of MWFs for chronic inhalation studies beginning back in 2000. As a result of a meeting July 27, 2005, a subsequent communication from NTP in August and a follow-up letter earlier referenced to
>
> Dr. Dan Morgan in October 2005, ILMA understood the complexities of the selection process which resulted. It began from a list of twenty-nine candidate fluids, then selection of nine fluids, and finally three from each class (synthetic, semi-synthetic and soluble oil) were selected for further evaluation. Each of these fluids differs widely from the others in formulation. Indeed, ILMA understands NTP believed TRIM® VX to be "unique" even among the six soluble oils evaluated.
>
> It is also clear that the results of the study can only apply to the tested article. OSHA, in its adoption of the Hazard Communication Standard "HCS 2012" notes how bridging principles might apply to read-across from mixtures that are tested and found to be carcinogenic. The following paragraphs are from 29 CFR 1910.1200, Appendix A, paragraphs A.6.3.2 and A.6.3.3:
>
> **A.6.3.2 Classification of mixtures when data are available for the complete mixture**
> A mixture may be classified based on the available test data for the mixture as a whole. In such cases, the test results for the mixture as a whole must be shown to be conclusive taking into account dose and other factors such as duration, observations and analysis (*e.g.*, statistical analysis, test sensitivity) of carcinogenicity test systems.
>
> **A.6.3.3 Classification of mixtures when data are not available for the complete mixture: bridging principles**
> Where the mixture itself has not been tested to determine its carcinogenic hazard, but there are sufficient data on both the individual ingredients and similar tested mixtures to adequately characterize the hazards of the mixture, these data will be used in accordance with the following bridging principles as found in paragraph A.0.5 of this Appendix: Dilution; Batching; and Substantially similar mixtures.

[4] Before NTP undertook its study of Trim® VX, ILMA provided a detailed explanation regarding the significant variations for MWFs. *See* ILMA letter to Dr. Daniel L. Morgan (October 21, 2005).

Application of these principles found in Appendix 6, Carcinogenicity, to other MWFs means that there cannot be an extension of the results to other MWFs unless other similarly composed MWFs also are found to show evidence of carcinogenicity and that there is found "sufficient data on...the individual ingredients" to allow such a conclusion to be drawn. The rules and principles contained within HCS 2012 do not allow for extrapolation or read-across of the results.

TRIM® VX is a Discontinued Product

ILMA reiterates that TRIM® VX is a unique, product that has been withdrawn from the marketplace by Master Chemicals. The Association understands that Master Chemical will comment to OEHHA on the product being no longer in use. Because TRIM® VX is not representative of MWFs generally and because the product is no longer in commerce, OEHHA should withdraw the proposed listing.[5] A Prop 65 listing only will cause confusion for MWF users in California.

Conclusion

Given the issues with the NTP study and the removal of the product from the marketplace, including in California, ILMA requests that OEHHA withdraw its Notice of Intent to list TRIM® VX on Prop 65. In the alternative, if OEHHA proceeds with the listing, the Association requests that OEHHA express clearly that TRIM® VX is a unique, discontinued product that may not be extrapolated to other MWF formulations.

Sincerely,

Holly Alfano
Chief Executive Officer

Enclosures: (3)

CC: ILMA MWF Committee
John K. Howell, Ph.D.
Jeffrey L. Leiter, Esq.
Daniel T. Bryant, Esq.

[5] This is inclusive of other TRIM branded products.

Enclosures

1. ILMA letter to Dr. Yun Xie – NTP Designated Federal Official (February 6, 2016).

2. ILMA letter to Dr. Yun Xie – NTP Designated Federal Official (December 13, 2016).

3. ILMA letter to Dr. Daniel L. Morgan (October 21, 2005).

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December 13, 2016

Via Overnight Delivery

Dr. Yun Xie
NTP Designated Federal Official
Office of Liaison, Policy, and Review
DNTP, NIEHS
P.O. Box 12233, MD-K2-03
Research Triangle Park, North Carolina 27709

RE: NTP's Final Technical Report for TRIM® VX

Dear Dr. Xie:

The Independent Lubricant Manufacturers Association ("ILMA" or "Association") submits these comments on the National Toxicology Program's ("NTP") Final Technical Report ("FTR") for its two-year inhalation study of the metalworking fluid ("MWF") TRIM® VX. ILMA previously submitted written comments on February 2, 2016, February 29, 2016, and March 21, 2016. Additionally, the Association participated in the Peer Review Panel ("Panel") meeting on February 16, 2016. While appreciative of the opportunity to participate in the FTR process, it appears that most of the Association and Peer Review Panel's recommendations and requested revisions were not incorporated in the FTR.

However, ILMA agrees with NTP's statement in the introduction to the FTR that "Formulations of metalworking fluids are continuously changing to improve functionality and reduce potential health and environmental concerns[1]." Further, ILMA concurs with NTP's statement in the foreword to the FTR that "Extrapolation of these results to other species, including characterization of hazards and risks to humans, requires analyses beyond the intent of these reports." Nevertheless, this conclusion should have been restated throughout the FTR.

While ILMA recognizes that it is unlikely the FTR will be further modified, the Association requests that this letter be included in the public docket.

ILMA's Previous Comments Regarding Product Life Were Not Appropriately Considered

ILMA provided NTP with a recommended "shelf life" for TRIM® VX. As previously stated in our February 2 comment letter:

> Despite the clear statement that the product had a recommended shelf life of 12 months, NTP began its study on a fluid that was already 8 months old and therefore many of the results came from an old, separated, and likely

[1] FTR at page 17-18.

> chemically altered version of TRIM® VX. Although not stated in the report, the age of each lot of TRIM® VX was approximately 7-8 months at the start of the respective studies. In 2005, ILMA sent a letter to Dr. Morgan at NIEHS stating that the recommended shelf life for MWFs from Master Chemical was 12 months. Given that the samples of TRIM® VX became substantially older than 12 months during the course of the studies, age-related separation and chemical alteration of the TRIM® VX could be expected. A number of compounds that were in the VX formula were not found in the NTP analysis and a number of measured components that were in the VX formula were reported at concentrations significantly different from the VX formula, possibly indicating degradation.

ILMA commented further on this issue in its March 21 letter:

> NTP did not provide an adequate explanation within the 2-year study to address the issues of degradation and separation. Master Chemical advised its customers that the product had a 12-month maximum shelf life; however, the samples that NTP utilized in the study were 30.5 months old at the conclusion. MWFs are unique formulations and the different components that comprise the mixture interact so differently that each product has a distinct lifespan. In an effort to ensure that NTP firmly understood the lifecycle of TRIM® VX, ILMA provided the information well in advance of the commencement of the study. The Association requests that a comment be made in the FTR that indicates that NTP was put on notice of the product's life span, and, despite that information, NTP elected to proceed with the study on a product significantly beyond its useful shelf life.

NTP did not appropriately note the issue with how old the product was during its 2-year study. The age of the product tested is highly relevant to the study and NTP's conclusions, and this issue should have been more conspicuously noted in the FTR.

Further, the March 21 letter presented concerns about the product testing that was similarly not well addressed:

> In addition, the lack of data presented regarding bacterial and fungal growth is particularly concerning. During the course of the [Peer Review] Panel discussion, there was much confusion about product testing in an attempt to clarify that the TRIM® VX samples did not become contaminated during the course of the study. The following exchange during the Panel meeting is particularly illuminating of this concern (Recording Segment #59 – Time Marker 20:58):
>
> **Dr. Brock:** So, in other words, you did the stability real-time with the unfrozen material by comparing it to the frozen sample? Do I understand that correctly?
>
> **Dr. Ryan:** Yes. So when we receive the test material at the time of receipt we take aliquots out and freeze them, so we can compare our data of all the test material throughout the study. And then we can compare the data currently compared to the reference sample so we have an understanding if there was any degradation over time.
>
> **Dr. Brock:** And it assumes that frozen samples over time don't degrade as well?
>
> **Dr. Ryan:** That is correct
>
> **Dr. Brock:** And did they?
>
> **Dr. Ryan:** I believe they were stored at appropriate conditions.
>
> **Dr. Brock:** Appropriate conditions. But did they degrade over time?

> **Dr. Ryan:** I don't think – no, we did not see any reference just looking at the frozen reference samples over time of any change as well.
>
> **Dr. Brock:** So you did the frozen sample stability over the duration of the study as well?
>
> **Dr. Ryan:** I believe so. Do you want to comment on that, Dr. –
>
> **NTP Scientist:** I just want clarify one thing, one editorial. It's not a frozen reference. The sample was stored at five degrees in the refrigerator.
>
> This statement is immensely problematic. MWFs are complex mixtures and must be stored carefully. These emulsions break down quickly under inappropriate storage conditions and causes the product to degrade and separate exponentially faster compared to when the product is stored properly.
>
> In essence, NTP's "test sample" or the control that served as the basis for comparison to ensure that the material was not degrading and separating was itself very likely degraded and separated. NTP should note this issue in its FTR.

Neither the "Materials and Methods" section[2] nor the "Chemical Characterization and Generation of Chamber Concentration" section[3] adequately addressed the concerns ILMA raised multiple times. The FTR does not even note that the "test sample" was inappropriately stored. This is highly disappointing and further calls into question NTP's conclusions.

The Aerosols Generated Were Not Representative of Occupational Exposures

ILMA addressed its concerns with the aerosols generated for the study in its February 2 letter:

> ILMA recommended that concentrates of soluble oil be diluted with water (1:20) before use in studies with laboratory animals. The reason, as stated by ILMA, is that "any change in product chemistry (including the possible reaction of water with other chemical components in the product concentrate) that might occur upon dilution would not occur if the soluble oil product concentrate were to be directly aspirated." While the use of undiluted concentrate had a definite advantage in terms of generating an aerosol without excessive humidity, the lack of dilution with water again raises a question of how representative the laboratory aerosol was of aerosols of this MWF in the workplace.

Indeed, NTP acknowledges that the aerosols generated for the study were done so for the sake of ease and are not representative of potential workplace exposures:

> Because it is technically difficult to generate and expose animals to liquid aerosols containing high water content, the metalworking fluid aerosols in the NTP studies were generated from undiluted concentrates and diluted with clean air to produce the desired concentrations. Thus, the exposure concentrations used in these studies were ***considerably higher*** than those encountered in an occupational setting[4]."[Emphasis added.]

This admission from NTP further calls into question the FTR's relevance and conclusions contained therein.

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[2] FTR at page 24.
[3] FTR at page 158.
[4] FTR at page 67.

NTP's Highest Dose Level Was Inappropriately Selected

In the March 21 letter it was noted:

> The highest dose level of 100 mg/m3 selected for two-year study was too high because fibrosis was seen in both male and female rats and mice at that level in the 90-day study; 50 mg/m3 would have been the more appropriate choice. Further, NTP's draft report notes on page 55 that "[t]he highest exposure concentration was based on the incidence and severity of lung fibrosis in the current 3-month study. Although minimal lung fibrosis was present in rats exposed to 50 and 100 mg/m3, this lesion was not expected to affect survival in the 2-year study, and use of the same exposure concentrations for rats and mice would facilitate inter-species comparisons. In addition, *these concentrations were used in the 2-year study of CIMSTAR® 3800 in Wistar Han rats, which allows for comparisons between the two metalworking fluid studies*" [emphasis added].

The increased incidence of tumors in mice only at 100 mg/m^3, the equivocal evidence of tumors in rats only at 100 mg/m3, the absence of trends for increased tumors at lower doses, the lack of positive results in genotoxicity screening assays of both TRIM® VX or some of its components, the lack of systemic tumors or toxicity, and the presence of significant non-neoplastic lesions in the respiratory tract (including fibrosis) collectively suggest a possible non-genotoxic mechanism for production of the observed tumors.

Dr. Brock also questioned the selection of 100 mg/m^3 dose level during his comments at the Panel meeting (Recording Segment #61 – Time Market 11:41):

Dr. Brock: For the study design, the dose levels used for the two-year bioassay in rats and mice were 10, 30, and a 100 mg/m3 and this is the result of the three- month chronic studies . . . Specifically the authors state that the high dose for the two-year studies was based on the occurrence of lung fibrosis in both species.

The incidences of severity of fibrosis at 50 and 100 mgs per cubic meter in rats and mice in the subchronic studies were essentially the same. Moreover, pathological findings at 50 and 100 mgs per cubic meter in rats and mice in the subchronic findings were quite similar. Therefore, it is the opinion of this reviewer that the high dose in the two-year studies were too high and an exposure concentration of 50 milligrams per cubic meter would have been sufficient for these studies. Unfortunately this cannot be corrected.

It is recommended, however, that the authors further describe in the discussion section dose selection based on the totality of the three-month data and the relevance of findings in the tox studies – this is weirdly written – relative to the doses used in the two-year study.

Ostensibly what I'm saying here is I think the dose levels were too high, particularly at the high dose, given the occurrence of fibrosis across all the doses in the three-month study. So you would expect some sort of fibrosis in the two- year study and of course you a get a carcinogenic outcome. I think that has to be discussed relative to dose level selection in greater detail than what's occurring in the report.

More troubling was the response to Dr. Brock's comments below (Recording Segment #61 – Time Marker 25:20):

Dr. Ryan: In addition -- we don't mention this -- these inhalation studies are quite large, and logistically it's helpful for us to have similar exposure concentrations. And as I already mentioned in the report, we also aimed to be able to do a comparison to CIMSTAR® 3800, which had these similar dose selections. So even though, you know, we did, you know, aim to look at all the data within three-month studies, we did focus in on those factors. And we can add more clarity.

Dr. Brock: Yeah. I can appreciate the complexity of two-year inhalation bioassays since I've done several of them. ***And to use the same concentrations for rats and mice because it's easier is not a good answer, you know*** [emphasis added]. I know NTP has used multiple -- different doses for different, for both species within the same study paradigms. So it still gets back to the concept of a much more robust dose justification and ultimately explaining the data for its carcinogenic outcome in the discussion section, relative to the dose levels that were selected.

NTP attempts to provide additional justification for its selection of the highest dose level, but Dr. Ryan's commentary during the Panel meeting was illuminating and seems to be the controlling justification for the concentrations selected. To reiterate Dr. Brock's point, "to use the same concentrations because it is easier . . . is not a good answer."

Comments from the Panel Were Not Adequately Addressed

Further, several members of the panel expressed concerns about the overall conclusions to be drawn from the two-year study and instructed NTP to include limiting language in the FTR:

> Dr. Jon Mirsalis (SRI International) commented on the selection of TRIM® VX and instructed that the FTR should include language that "a relatively small volume of it [TRIM® VX] was in use, and it has since been discontinued. He noted that wider conclusions about soluble MWFs **should not and could not be drawn based on this study, which stands on its own."** [emphasis added].
>
> Dr. John Bucher (Associate Director of NTP) added "[i]t was difficult to select materials for 2-year study that would give some indication of whether some of the effects that were seen in the MWFs could be attributed to materials that were not contaminated with bacteria during the course of their use. **Due to the complexity of the field, the materials chosen are not representative, but are individual materials."** [emphasis added].

These statements are paramount. While NTP made some effort to qualify the results, a statement that clearly articulated the points Dr. Bucher and Dr. Mirsalis made should have been included in the introduction. Further, more conspicuous statements to that effect should have been included throughout the FTR.

TRIM® VX Is A Unique Formulation and Is Not Representative

In the February 2 comment letter, ILMA noted that the bridging principles outlined in the Occupational Safety and Health Administration's (OSHA) Hazard Communication Standard 2012 do not allow for extrapolation of the results from this study to be applied to other MWFs:

> NTP is aware that MWFs are complex mixtures, that the substances in MWFs vary considerably and that thousands of formulations are commercially available. Indeed, it was just these circumstances that resulted in NTP and NIOSH collaborating on a selection process of MWFs for chronic inhalation studies beginning back in 2000. As a result of a meeting July 27, 2005, a subsequent communication from NTP in August and a follow-up letter earlier referenced to Dr. Dan Morgan in October, 2005, ILMA understood the complexities of the selection process which resulted. It began from a list of twenty-nine candidate fluids, then selection of nine fluids, and finally three from each class (synthetic, semi-synthetic

and soluble oil) were selected for further evaluation. Each of these fluids differs widely from the others in formulation. Indeed, ILMA understands NTP believed TRIM® VX to be "unique" even among the six soluble oils evaluated.

It is also clear that the results of the study can only apply to the tested article. The Occupational Safety and Health Administration ("OSHA"), in its adoption of the Hazard Communication Standard "HCS 2012" notes how bridging principles might apply to read-across from mixtures that are tested and found to be carcinogenic. The following paragraphs are from 29 CFR 1910.1200, Appendix A, paragraphs A.6.3.2 and A.6.3.3:

A.6.3.2 Classification of mixtures when data are available for the complete mixture

A mixture may be classified based on the available test data for the mixture as a whole. In such cases, the test results for the mixture as a whole must be shown to be conclusive taking into account dose and other factors such as duration, observations and analysis (*e.g.*, statistical analysis, test sensitivity) of carcinogenicity test systems.

A.6.3.3 Classification of mixtures when data are not available for the complete mixture: bridging principles

Where the mixture itself has not been tested to determine its carcinogenic hazard, but there are sufficient data on both the individual ingredients and similar tested mixtures to adequately characterize the hazards of the mixture, these data will be used in accordance with the following bridging principles as found in paragraph A.0.5 of this Appendix: Dilution; Batching; and Substantially similar mixtures.

Application of these principles found in Appendix 6, Carcinogenicity, to other MWFs means that there cannot be an extension of the results to other MWFs unless other similarly composed MWFs also are found to show evidence of carcinogenicity and that there is found "sufficient data on...the individual ingredients" to allow such a conclusion to be drawn.

The rules and principles contained within HCS 2012 do not allow for extrapolation or read-across of the results. The Association laments that this point was not made more clearly in the FTR.

Conclusion

While ILMA appreciates the opportunity to participate in the NTP's public process on the FTR, the Association's recommendations and the Peer Review Panel's directives should have been more clearly articulated by NTP. Finally, TRIM® VX was a low-volume mixture that is not representative of soluble oil MWFs or MWFs generally. It is a unique formulation, and NTP's study and its conclusions are unique to TRIM® VX, and only TRIM® VX.

Sincerely,

Holly Alfano

Holly Alfano
CEO

ilma
Independent Lubricant Manufacturers Association

February 2, 2016

Via Electronic Mail

Dr. Yun Xie
NTP Designated Federal Official
Office of Liaison, Policy, and Review
P.O. Box 12233, MD-K2-03
Research Triangle Park, North Carolina 27709

Re: National Toxicology Program's Technical Report for TRIM® VX

Dear Dr. Xie:

The Independent Lubricant Manufacturers Association ("ILMA" or "Association") submits the following comments, along with a review ("Review") of the National Toxicology Program's ("NTP") draft Technical Report ("Report") on toxicological studies of TRIM® VX for which the peer review panel will meet on February 16, 2016. Dr. Wally Dalbey, M.A. Ph.D., D.A.B.T., DalbeyTox, LLC, West Chester, PA performed the Review. The Review contains comments and suggestions, which ILMA requests NTP consider as it finalizes its Report.

The Review outlines comments in the order of NTP's Report. The comments contained herein highlight some of Dr. Dalbey's comments contained within the Review. The fully-indented comments are Dr. Dalbey's while the non-indented comments are directly from ILMA. ILMA also comments on the possible extension of the results to other metalworking fluids ("MWFs") and the validity of the overall study conducted by NTP on TRIM® VX.

Introduction to ILMA

ILMA is national trade association with 338 member companies. As a group, ILMA members blend, compound, and sell over 25 percent of the United States' lubricant needs (e.g. passenger car motor oils) and nearly 80 percent of the MWFs utilized in the country. Independent lubricant manufacturers by definition are neither owned nor controlled by companies that explore for or refine crude oil to produce lubricant base stocks or that produce chemical additives. Base oils are purchased from refiners, who also are competitors in the sale of finished products. Additives are purchased from suppliers, who also may be competitors in the sale of finished products. ILMA members succeed by processing, producing, and distributing high-quality, often specialized, lubricants.

Highlights of the Review and Issues with NTP's Report and Conclusions

ILMA has concerns about the manner in which the study was conducted and the conclusions reached by NTP in its study of TRIM® VX. In the Report, NTP outlines its conclusions[1] of two instances of "equivocal evidence" and two instances of "clear evidence". Although the tumor incidences and statistical analyses in the Report appear to be appropriate, ILMA does not believe that NTP's conclusions are consistent with the definitions for those

terms as outlined in the Report. NTP should conclude this Report to be an "inadequate study[2]." ILMA's contention is that the results cannot be interpreted as showing the presence or absence of carcinogenic activity because that tested sample of TRIM® VX was handled in such a way that the aerosol used in the two-year study no longer adequately represented TRIM® VX.

Not all metal working fluids cause symptoms associated with respiratory irritation. NTP asserts on page 25, "[o]ccupational exposure to metalworking aerosol is associated with a variety of nonmalignant respiratory and dermal conditions. . ." As currently written, NTP's statement is misleading.

> **Page 25, 1st and 3rd lines under "Humans":** Please consider changing "exposure to metalworking fluid aerosols" to "exposure to some metalworking fluid aerosols" or similar wording here and elsewhere to avoid implying that all MWFs are associated with nonneoplastic effects including bronchitis and asthma.

Further elaboration is needed as to why TRIM® VX was selected for a two-year study. Additionally, NTP must correct its contention that TRIM® VX has a high production volume.

> **Page 31,** selection of TRIM® VX: A statement is made that TRIM® VX was selected for 2-year studies based on the incidence of fibrosis of the lung during 3-month studies; TRIM® VX was the only metalworking fluid with this lesion. Please elucidate why pulmonary fibrosis made TRIM® VX a candidate for a carcinogenicity study. That is, given that fibrosis had already been demonstrated, was there an underlying rationale for selecting TRIM® VX for a carcinogenicity study? As stated in the report, "In rats and mice, pulmonary fibrosis is a common response to particulate exposure and is usually associated with areas of chronic injury and inflammation (NTP, 1998, 2001, 2002)". Given this and the facts that the screening assays for genetic toxicity were negative, it would seem that a nongenotoxic mechanism for tumorigenesis might be relevant. Was this considered?
>
> Also related to the selection of TRIM® VX, the report states in the abstract and elsewhere that TRIM® VX has a high production volume. However, this product is considered by the manufacturer to be a low-volume product. Please correct these statements.

---

[1] "Under the conditions of these 2-year inhalation studies, there was equivocal evidence of carcinogenic activity of TRIM VX in male Wistar Han rats based on the combined occurrences of alveolar/bronchiolar adenoma or carcinoma of the lung. There was equivocal evidence of carcinogenic activity of TRIM VX in female Wistar Han rats based on the occurrences of alveolar/bronchiolar adenoma of the lung. There was clear evidence of carcinogenic activity of TRIM VX in male B6C3F1/N mice based on the increased combined incidences of alveolar/bronchiolar adenoma or carcinoma of the lung. There was clear evidence of carcinogenic activity of TRIM VX in female B6C3F1/N mice based on the increased combined incidences of alveolar/bronchiolar adenoma or carcinoma (primarily carcinoma) of the lung."

[2] NTP defines the term as: "[i]nadequate study of carcinogenic activity is demonstrated by studies that, because of major qualitative or quantitative limitations, cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity."

ILMA requests that NTP provide the data regarding bacteria and fungi growth, as this information is critical and necessary to understand and interpret the study. Without that information, there are serious questions regarding the validity of NTP's conclusions.

Page 33: The report states that "amounts of bacteria and fungi were also determined". However, results were not presented in the report or provided when requested by ILMA. Because of the known growth of bacteria and fungi in MWF, this information is significant in the interpretation of the study. Master Chemical Corporation will submit further comments on this issue.

Clarification is needed on the analyzed composition of TRIM® VX, such as an explicit statement on the relation between hexane-extractable material and mineral oil. Acknowledgement that the composition of a significant fraction of the MWF was not determined would also be beneficial.

Page 33, bottom: The neat MWF was found to contain mainly "water, alkanolamines, and oil". Although not explicitly stated, the report is written as though the hexane-extractable fraction was equivalent to mineral oil. Was that the intent? If so, that assumption needs to be stated clearly.

However, the MSDS for TRIM® VX states that severely hydrotreated petroleum oil was present in the MWF at 30-40%, as opposed to the 85% reported by NTP for hexane-extractable material (HEM). Apparently constituents other than mineral oil were in the HEM. Revision A of EPA Method 1664 (the method cited in Appendix H under characterization of TRIM® VX) states that the hexane extract can include relatively non-volatile hydrocarbons, vegetable oils, animal fats, waxes, soaps, greases, and related materials. It does not appear that any further characterization was performed on the extract of TRIM® VX to determine its composition. Clarification of the relation between HEM and mineral oil is needed. Master Chemical Corporation will submit additional comments on this subject.

The measured component parts in Table 1 on page 34 total 109.68% for Lot 101607Nb and 110.08% for Lot 011509Nc. An explanation is needed for the variation in totals.

Page 34, Table 1: The totals of the analyzed constituents were 109.68% for Lot 101607Nb and 110.08% for Lot 011509Nc. Were those totals considered to be within the acceptable boundaries of accuracy?

Given that no changes were made by the producer in the formulation of the two lots, were the differences in analyzed percentages for specific substances between the lots within acceptable boundaries (especially for chlorocresol)? If the numbers in Table 1 represent more than one analysis, how much variation was **seen among multiple analyses?**

There is a significant discrepancy with the pH from NTP and the pH from the Material Safety Data Sheet from Master Chemical for TRIM® VX. This discrepancy is a serious issue and requires explanation from NTP. Further, this raises yet another question as to what substance NTP actually tested given the significant pH variation.

Page 33, bottom: The report gives the pH of TRIM® VX as approximately 7.5. There are multiple issues with this result. First, was the pH from NTP performed on undiluted TRIM® VX and does NTP consider

the pH of 7.5 to be a valid observation? According to the MSDS, the pH of a 10% solution of TRIM® VX is in the range of 8.3 to 9.3, while the pH of the undiluted MWF is not applicable due to the small amount of water present. Undiluted TRIM® VX has very little water in it and can be considered close to a nonaqueous solution. It is well known that determination of pH can be done on nonaqueous solutions, but not by the same method that is used for aqueous solutions (http://www.iupac.org/publications/analytical compendium/Cha03sec5.pdf). Appendix H states only that an "industry-standard" method for determination of pH was used. Assuming that the typical method for aqueous solutions was used, the accuracy of the reported pH is highly questionable.

If the pH of 7.5 was determined on diluted TRIM® VX, then that value is at odds with the manufacturer's typical value for a 10% dilution and one must consider possible alteration of the sample on which the pH was measured (see comments on uniformity of the sample and on shelf life) or an inaccurate pH reading.

A pH of 7.5 might give the impression that the pH of the aerosol of TRIM® VX was near neutrality. However, with a pH in the range of 8.3-9.3 for diluted TRIM® VX, one could expect that aerosol deposited in the respiratory tract would produce an alkaline mixture after it meets water in the epithelium. The resulting alkalinity could be a factor in the production of the nonneoplastic lesions observed in these studies.

The discrepancy between 7.5 and 8.3-9.3 is significant because, in addition to the resulting questions on methodology, pH is an important property of the MWF and might have significance on the effects observed in the respiratory tract.

NTP's must provide a clarification and an explanation for the manner in which the aerosol concentrations were monitored during the study.

Page 35, monitoring aerosol concentration: The real-time aerosol monitors (RAMs) used to monitor the aerosol concentrations were calibrated against the levels of methyl palmitate, methyl stearate, and methyl oleate collected on adsorbent gas sampling tubes and measured by GC/FID. The description of this method is incomplete. More specifically…

- Why was this method chosen for calibration rather than gravimetric sampling of the aerosol?
- Were the gas sampling tubes demonstrated to collect all of the airborne fatty acids without breakthrough?
- Was it demonstrated that the fatty acid methyl esters collected in this manner were a consistent percentage of the airborne MWF and that those percentages were the same as in the undiluted MWF?
- The totals of these fatty acids were 7.72% of the lot used in the 3-month studies and 7.94% of the lot used in the 2-year study. Were those numbers used for each study?
- Were corrections for evaporation of water (7% of the neat MWF) or other volatile components needed during calculation of total aerosol mass? Presumably much of the water would evaporate.
- Appendix H on chemical characterization and generation of chamber concentrations did not contain sufficient additional details to address these questions.

NTP should provide an explanation that accounts for the variation and change of propylene glycol.

Page 37, stability: Judging from this section, it sounds as though the relative amount of propylene glycol changed fairly consistently. According to a Dow website (http://msdssearch.dow.com/PublishedLiteratureDOWCOM/dh_091b/0901b8038091b508.pdf?filepath=propyleneglycol/pdfs/noreg/117-01682.pdf&fromPage=GetDoc), its vapor pressure is 0.13 mm Hg at 25°C. That's not particularly high and the glycol is only 0.2% of the neat MWF, but did some vaporize from the aerosol during or after aerosolization? Measurement of a vapor phase was not referenced in Appendix H.

ILMA provided NTP with a recommended shelf life for TRIM® VX well in advance of this study. Despite the clear statement that the product had a recommended shelf life of 12 months, NTP began its study on a fluid that was already 8 months old and therefore many of the results came from an old, separated, and likely chemically altered version of TRIM® VX.

Page 37, related comment on age of fluid: Although not stated in the report, the age of each lot of TRIM® VX was approximately 7-8 months at the start of the respective studies. In 2005, ILMA sent a letter to Dr. Morgan at NIEHS stating that the recommended shelf life for MWFs from Master Chemical was 12 months. Given that the samples of TRIM® VX became substantially older than 12 months during the course of the studies, age-related separation and chemical alteration of the TRIM® VX could be expected. A number of compounds that were in the VX formula were not found in the NTP analysis and a number of measured components that were in the VX formula were reported at concentrations significantly different from the VX formula, possibly indicating degradation and raising the question of how well the laboratory aerosol represented workplace aerosols for this MWF.

Given the recommended dilution of TRIM® VX and that NTP did not dilute the product to that recommended level, there are serious issues about how representative the laboratory tests are of real-world exposures to TRIM® VX.

Page 37, related comment on dilution of fluid: In the same letter, ILMA recommended that concentrates of soluble oil be diluted with water (1:20) before use in studies with laboratory animals. The reason, as stated by ILMA, is that "any change in product chemistry (including the possible reaction of water with other chemical components in the product concentrate) that might occur upon dilution would not occur if the soluble oil product concentrate were to be directly aspirated". While the use of undiluted concentrate had a definite advantage in terms of generating an aerosol without excessive humidity, the lack of dilution with water again raises a question of how representative the laboratory aerosol was of aerosols of this MWF in the workplace.

Master provides explicit instructions for proper handling and storage of TRIM® VX; however, the Report does not offer sufficient detail to ensure that those handling and storage practices were followed throughout the duration of the study. This raises serious concerns about the fluids composition during the study and the subsequent testing and conclusions drawn therefrom.

Appendix H, Figure H2: The diagram depicts an Exposure Chemical Cabinet where the drum of TRIM VX was located. Was the material dispensed directly from the original drum? Can you provide details on

the mixing apparatus, e.g., the depth and strength of the mixer and its ability to maintain uniform composition of the TRIM VX? Basically, what information is available to verify that the uniformity of the MWF was maintained in the drum during the 2-year study?

NTP should find the study to be an "Inadequate Study."

In the paragraphs above, ILMA has identified numerous deficiencies with the characterization of the actual aerosol to which the animals were exposed, such as information regarding possible bacterial and fungal growth. This is particularly troubling as ILMA is aware that this product is especially prone to growth of fungus. If fungus had grown in the fluid to which the animals were exposed, any finding cannot be attributed to TRIM® VX. Additionally, the variations in the chemical characterization of TRIM® VX, including missing chemical compounds that were formulated into the product, variation in other components, significant variation in pH, variability in propylene glycol concentration, taken together, strongly suggest that the chemical composition of the product had changed, further suggesting that any finding cannot be attributed to TRIM® VX. Finally, NTP used the product well beyond its stated shelf life. ILMA is aware that as the product ages, stratification of the product can occur resulting in a composition which varies depending upon the part of the container from which it was drawn. Taken together, all of these issues surrounding the identification of the substance to which the animals were exposed strongly suggest that NTP can only conclude that this study is Inadequate.

If NTP will not conclude that the study is an "Inadequate Study," NTP should not extend the results of this study to other MWFs.

NTP is aware that MWFs are complex mixtures, that the substances in MWFs vary considerably and that thousands of formulations are commercially available. Indeed, it was just these circumstances that resulted in NTP and NIOSH collaborating on a selection process of MWFs for chronic inhalation studies beginning back in 2000. As a result of a meeting July 27, 2005, a subsequent communication from NTP in August and a follow-up letter earlier referenced to Dr. Dan Morgan in October, 2005, ILMA understood the complexities of the selection process which resulted. It began from a list of twenty-nine candidate fluids, then selection of nine fluids, and finally three from each class (synthetic, semi-synthetic and soluble oil) were selected for further evaluation. Each of these fluids differs widely from the others in formulation. Indeed, ILMA understands NTP believed TRIM® VX to be "unique" even among the six soluble oils evaluated.

It is imperative that the questions raised by Dr. Dalbey be fully addressed. Further, as noted above, ILMA strongly believes that NTP should find the study to be Inadequate. But, whatever NTP decides, it is also clear that the results of the study can only apply to the tested article. The Occupational Safety and Health Administration ("OSHA"), in its adoption of the Hazard Communication Standard "HCS 2012" notes how bridging principles might apply to read-across from mixtures that are tested and found to be carcinogenic. The following paragraphs are from 29 CFR 1910.1200, Appendix A, paragraphs A.6.3.2 and A.6.3.3:

A.6.3.2 Classification of mixtures when data are available for the complete mixture

A mixture may be classified based on the available test data for the mixture as a whole. In such cases, the test results for the mixture as a whole must be shown to be conclusive taking into account dose

and other factors such as duration, observations and analysis (e.g., statistical analysis, test sensitivity) of carcinogenicity test systems.

A.6.3.3 Classification of mixtures when data are not available for the complete mixture: bridging principles

Where the mixture itself has not been tested to determine its carcinogenic hazard, but there are sufficient data on both the individual ingredients and similar tested mixtures to adequately characterize the hazards of the mixture, these data will be used in accordance with the following bridging principles as found in paragraph A.0.5 of this Appendix: Dilution; Batching; and Substantially similar mixtures.

For purposes of classification and labeling, guidance is available from OSHA's HCS 2012. While there are more general bridging rules discussed elsewhere in Appendix A, application of these principles found in Appendix 6, Carcinogenicity, to other MWFs means that there cannot be an extension of the results to other MWFs unless other similarly composed MWFs also are found to show evidence of carcinogenicity and that there is found "sufficient data on…the individual ingredients" to allow such a conclusion to be drawn.

Conclusion

ILMA appreciates this opportunity to provide comments on NTP's Report and respectfully requests that due consideration be given to the comments contained above and in the full Review from Dr. Dalbey. Additionally, ILMA would welcome the opportunity for a further dialogue to clarify any lingering questions or comments once NTP has an opportunity to digest the Review in its entirety.

Sincerely,

Holly Alfano
Chief Executive Officer

Enclosures: Dr. Wally Dalbey's Review
ILMA's 2005 Letter to Dr. Dan Morgan

cc: ILMA Board of Directors
ILMA Metalworking Fluids Committee
John K. Howell, Ph.D.
Jeffrey L. Leiter, Esq.
Daniel T. Bryant, Esq.

Review of NTP Technical Report on the Toxicology and Carcinogenesis Studies of TRIM® VX in Wistar Han [Crl:WI (Han)] Rats and B6C3F1/N Mice (Inhalation Studies) NTP TR 591

Performed by DalbeyTox, LLC

Walden Dalbey. MA, PhD, DABT

February 1, 2016

The following pages contain comments made by DalbeyTox, LLC during a review of the NTP report (NTP TR 591) on toxicology and carcinogenicity studies with TRIM® VX, a soluble oil metalworking fluid (MWF). DalbeyTox, LLC performed this work under an agreement with the Independent Lubricant Manufacturers Association (ILMA).

Overall, the report is well written and the conclusions on potential carcinogenic activity are consistent with NTP's criteria. However, we do have the following specific comments, particularly on how the conduct of the study could have limited the application of the results. We hope that NTP will be able to address these comments.

Page 20: The biocide 4-chloro-3-methylphenol (chlorocresol, CASRN 59-50-7) was identified as a component in TRIM® VX and, on page 34, its analyzed concentration was 2.49 and 3.59 in two lots of the MWF. The actual concentration of chlorocresol in TRIM® VX is 1.9% based on information provided by Master Chemical Corporation.

Page 20: The MSDS for TRIM® VX has statements indicating that the undiluted concentrate was both a dermal irritant and an ocular irritant. When animals are exposed to a high aerosol concentration of this MWF, one might expect some type of irritant reaction, including observable nonneoplastic changes.

Page 25, 1st and 3rd lines under "Humans": Please consider changing "exposure to metalworking fluid aerosols" to "exposure to some metalworking fluid aerosols" or similar wording here and elsewhere to avoid implying that all MWFs are associated with nonneoplastic effects including bronchitis and asthma.

Page 27, lines 8-9 under "Experimental Animals": The statement related to Jepsen et al (1977) is that the "incidences of skin papillomas (40% to 100%) were more pronounced in mice treated with undiluted (i.e., straight oil) metalworking fluids versus diluted (i.e., solvent-extract) versions." In fact, one straight oil in this article was solvent extracted and the one oil that was diluted to form an emulsion did not appear to have a solvent-extracted mineral oil. Solvent extraction refers to a process for removal of polycyclic aromatic compounds (PACs) from the oil, apparently not performed well enough in Jepsen's 1977 study to produce highly refined (noncarcinogenic) oils. Solvent extraction is not related to dilution.

Page 31, selection of TRIM® VX: A statement is made that TRIM® VX was selected for 2-year studies based on the incidence of fibrosis of the lung during 3-month studies; TRIM® VX was the only metalworking fluid with this lesion. Please elucidate why pulmonary fibrosis made TRIM® VX a candidate for a carcinogenicity study. That is, given that fibrosis had already been demonstrated, was there an underlying rationale for selecting TRIM® VX for a carcinogenicity study? As stated in the report, "In rats and mice, pulmonary fibrosis is a common response to particulate exposure and is usually associated with areas of chronic injury and inflammation (NTP, 1998, 2001, 2002)". Given this and the facts that the screening assays for genetic toxicity were negative, it would seem that a nongenotoxic mechanism for tumorigenesis might be relevant. Was this considered?

Also related to the selection of TRIM® VX, the report states in the abstract and elsewhere that TRIM® VX has a high production volume. However, this product is considered by the manufacturer to be a low volume product. Please correct these statements.

Page 33: The report states that "amounts of bacteria and fungi were also determined". However, results were not presented in the report or provided when requested by ILMA. Because of the known growth of bacteria and fungi in MWF, this information is significant in the interpretation of the study. Master Chemical Corporation will submit further comments on this issue.

Page 33, bottom: The neat MWF was found to contain mainly "water, alkanolamines, and oil". Although not explicitly stated, the report is written as though the hexane-extractable fraction was equivalent to mineral oil. Was that the intent? If so, that assumption needs to be stated clearly.

However, the MSDS for TRIM® VX states that severely hydrotreated petroleum oil was present in the MWF at 30-40%, as opposed to the 85% reported by NTP for hexane-extractable material (HEM). Apparently constituents other than mineral oil were in the HEM. Revision A of EPA Method 1664 (the method cited in Appendix H under characterization of TRIM® VX) states that the hexane extract can include relatively non-volatile hydrocarbons, vegetable oils, animal fats, waxes, soaps, greases, and related materials. It does not appear that any further characterization was performed on the extract of TRIM® VX to determine its composition. Clarification of the relation between HEM and mineral oil is needed.

Master Chemical Corporation will submit additional comments on this subject.

Page 34, Table 1: Given that the potential carcinogenicity of mineral oils is related their content of PACs and that mineral oil was the significant portion of the tested MWF, was information obtained from either Master Chemical or was further testing performed on the composition or biological activity of the mineral oil?

Page 34, Table 1: The totals of the analyzed constituents were 109.68% for Lot 101607Nb and 110.08% for Lot 011509Nc. Were those totals considered to be within the acceptable boundaries of accuracy?

Given that no changes were made by the producer in the formulation of the two lots, were the differences in analyzed percentages for specific substances between the lots within acceptable boundaries (especially for chlorocresol)? If the numbers in Table 1 represent more than one analysis, how much variation was seen among multiple analyses?

Page 33, bottom: The report gives the pH of TRIM® VX as approximately 7.5. There are multiple issues with this result. First, was the pH from NTP performed on undiluted TRIM® VX and does NTP consider the pH of 7.5 to be a valid observation? According to the MSDS, the pH of a 10% solution of TRIM® VX is in the range of 8.3 to 9.3, while the pH of the undiluted MWF is not applicable due to the small amount of water present. Undiluted TRIM® VX has very little water in it and can be considered close to a nonaqueous solution. It is well known that determination of pH can be done on nonaqueous solutions, but not by the same method that is used for aqueous solutions (http://www.iupac.org/publications/analytical compendium/Cha03sec5.pdf). Appendix H states only that an "industry-standard" method for determination of pH was used. Assuming that the typical method for aqueous solutions was used, the accuracy of the reported pH is highly questionable.

If the pH of 7.5 was determined on diluted TRIM® VX, then that value is at odds with the manufacturer's typical value for a 10% dilution and one must consider possible

alteration of the sample on which the pH was measured (see comments on uniformity of the sample and on shelf life) or an inaccurate pH reading.

A pH of 7.5 might give the impression that the pH of the aerosol of TRIM® VX was near neutrality. However, with a pH in the range of 8.3-9.3 for diluted TRIM® VX, one could expect that aerosol deposited in the respiratory tract would produce an alkaline mixture after it meets water in the epithelium. The resulting alkalinity could be a factor in the production of the nonneoplastic lesions observed in these studies.

The discrepancy between 7.5 and 8.3-9.3 is significant because, in addition to the resulting questions on methodology, pH is an important property of the MWF and might have significance on the effects observed in the respiratory tract.

Page 35, aerosol generation: The report does not clearly indicate if the MWF was diluted with water before being pumped into the aerosol generator. A clear statement to that effect would help readers who are accustomed to dilution of similar MWFs.

Page 35, monitoring aerosol concentration: The real-time aerosol monitors (RAMs) used to monitor the aerosol concentrations were calibrated against the levels of methyl palmitate, methyl stearate, and methyl oleate collected on adsorbent gas sampling tubes and measured by GC/FID. The description of this method is incomplete. More specifically...

- Why was this method chosen for calibration rather than gravimetric sampling of the aerosol?
- Were the gas sampling tubes demonstrated to collect all of the airborne fatty acids without breakthrough?
- Was it demonstrated that the fatty acid methyl esters collected in this manner were a consistent percentage of the airborne MWF and that those percentages were the same as in the undiluted MWF?
- The totals of these fatty acids were 7.72% of the lot used in the 3-month studies and 7.94% of the lot used in the 2-year study. Were those numbers used for each study?
- Were corrections for evaporation of water (7% of the neat MWF) or other volatile components needed during calculation of total aerosol mass? Presumably much of the water would evaporate.
- Appendix H on chemical characterization and generation of chamber concentrations did not contain sufficient additional details to address these questions.

Page 36, Characterization of chamber atmosphere: As with the measurement of total aerosol concentration, the measurement of particle size again assumes that the concentration of methyl oleate (the analyzed marker for aerosol measured in impactor samples) is the same in both the aerosol and the neat MWF. Data or a stated rationale to support this assumption is needed.

Page 37, stability: Judging from this section, it sounds as though the relative amount of propylene glycol changed fairly consistently. According to a Dow website (http://msdssearch.dow.com/PublishedLiteratureDOWCOM/dh_091b/0901b8038091b508.pdf?filepath=propyleneglycol/pdfs/noreg/117-01682.pdf&fromPage=GetDoc), its vapor pressure is 0.13 mm Hg at 25°C. That's not particularly high and the glycol

is only 0.2% of the neat MWF, but did some vaporize from the aerosol during or after aerosolization? Measurement of a vapor phase was not referenced in Appendix H.

Page 37, related comment on age of fluid: Although not stated in the report, the age of each lot of TRIM® VX was approximately 7-8 months at the start of the respective studies. In 2005, ILMA sent a letter to Dr. Morgan at NIEHS stating that the recommended shelf life for MWFs from Master Chemical was 12 months. Given that the samples of TRIM® VX became substantially older than 12 months during the course of the studies, age-related separation and chemical alteration of the TRIM® VX could be expected. A number of compounds that were in the VX formula were not found in the NTP analysis and a number of measured components that were in the VX formula were reported at concentrations significantly different from the VX formula, possibly indicating degradation and raising the question of how well the laboratory aerosol represented workplace aerosols for this MWF.

Page 37, related comment on dilution of fluid: In the same letter, ILMA recommended that concentrates of soluble oil be diluted with water (1:20) before use in studies with laboratory animals. The reason, as stated by ILMA, is that "any change in product chemistry (including the possible reaction of water with other chemical components in the product concentrate) that might occur upon dilution would not occur if the soluble oil product concentrate were to be directly aspirated". While the use of undiluted concentrate had a definite advantage in terms of generating an aerosol without excessive humidity, the lack of dilution with water again raises a question of how representative the laboratory aerosol was of aerosols of this MWF in the workplace.

Appendix H, Figure H2: The diagram depicts an Exposure Chemical Cabinet where the drum of TRIM VX was located. Was the material dispensed directly from the original drum? Can you provide details on the mixing apparatus, e.g., the depth and strength of the mixer and its ability to maintain uniform composition of the TRIM VX? Basically, what information is available to verify that the uniformity of the MWF was maintained in the drum during the 2-year study?

Page 62 and following pages, Pathology and statistical analyses in rats: In the preliminary release of statistical summaries by NTP on the internet, several statistically significant differences between exposed groups and the concurrent controls were noted in which tumor incidence was significantly lower in the treated groups (summarized below). While these differences do not influence the main conclusions from the studies, some mention of them in the report might help readers better appreciate the variability that can occur in the bioassay.

Male rats: Adenomas in pancreatic islets
Female rats: Adenomas in pituitary gland, stromal polyp in uterus, benign tumors in all organs
Male mice: None
Female mice: Carcinomas in pituitary gland

Page 70: Based on the preliminary release of statistical summaries by NTP on the internet, male rats had a statistically significant higher incidence of adenomas in thyroid follicular cells, but only with the middle dose. Please consider mentioning this incidence and the lack of a dose-response in the report.

Page 94: A statement is made that the fibrosis observed in the 3-month study was caused by the chemical constituents of TRIM® VX. Please consider changing the

wording to "chemical or physical properties of TRIM VX aerosolized in this study" because the mechanism of fibrosis is not known.

Page 98: As stated on page 98 and elsewhere in the report, the concentration-related nonneoplastic lesions might have contributed to the development of pulmonary tumors. In that vein, please consider the following. The increased incidence of pulmonary tumors in mice occurred only at 100 mg/m^3. Equivocal evidence of tumors in rats also occurred only at 100 mg/m^3. No trends were observed for increased tumor incidence in either species exposed to lower concentrations. *In vitro* genotoxicity assays and *in vivo* micronucleus tests were negative with TRIM® VX, as were mutagenicity tests on components of TRIM® VX (page 100). Collectively these results are suggestive of a nongenotoxic mechanism involving irritant or other nonspecific properties of the aerosol and possibly having a threshold. Can NTP address this possibility?

For comparison, has NTP performed other studies in which similar nonneoplastic lesions were found with aerosols at approximately 100 mg/m3, not just in the nature of the lesions but also in severity? Was an increased incidence of alveolar/bronchiolar tumors seen in these studies? Were the screening tests for genotoxicity also negative for those test substances? (We are trying to gain a better understanding of the possible MOA.)

Page 100: The report states "evidence of systemic toxicity or carcinogenicity was not observed in animals exposed to TRIM VX, which implies that TRIM VX-related toxicity may be limited to the site of contact." Depending on how this wording is interpreted, it can be confusing since evidence of carcinogenicity was actually observed. Do you mean to say "evidence of systemic toxicity or systemic carcinogenicity was not observed…"?

Discussion: Given the general lack of effects in the 3-month studies at concentrations at or below 100 mg/m3 (aside from spleens in male mice) and the lack of increased systemic tumors in the 2-year studies, a more explicit statement about the systemic toxicity of TRIM® VX would be appropriate. More can be said on the idea that the main effects appear to be confined to the point of contact in the body.

INDEPENDENT LUBRICANT MANUFACTURERS ASSOCIATION

October 21, 2005

Dr. Daniel L. Morgan
Respiratory Toxicology
NIEHS
P.O. Box 12233
Research Triangle Park, NC 27709

Dear Dr. Morgan:

I am writing this letter to follow-up on the July 27, 2005 meeting between staff from the National Toxicology Program (NTP) and representatives from the Independent Lubricant Manufacturers Association (ILMA). At this meeting, we discussed the status of NTP's Cancer Bioassay studies of nine metalworking fluids (MWFs) and explored ways that ILMA could assist NTP with its research endeavors by providing practical insights about these products and their commercial uses.

Thank you for hosting the meeting. It went a long way to establishing open lines of communication between ILMA and NTP. We learned a great deal and look forward to assisting NTP as much as possible.

At the meeting, we agreed to a mutual information exchange. To assist NTP in designing further studies, ILMA agreed to provide technical product specifications on shelf life and fluid stability, insights on dilution, and to explore whether we could provide information *related* to product formulation, short of the actual product formulas. (We are pleased that NTP recognizes that the disclosure of actual product formulas would be exceedingly difficult because they are trade secrets in a highly-competitive market.)

NTP agreed to provide ILMA a summary of the factors and underlying reasoning that it considered in selecting the nine fluids for study (NTP's "selection criteria"). As we noted at the meeting, the plurality of products in the MWF market (in terms of chemical composition and application) precludes identifying a "representative" sampling of MWFs. The fluids are unique in the truest sense of the word. ILMA agreed, nevertheless, to provide some feedback on NTP's selection criteria. Several weeks ago you shared the selection criteria with us.

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Product Specifications

The following matrix addresses shelf life and product stability for the nine fluids assuming normal storage conditions:

PRODUCT LINE	SHELF LIFE	STABILITY
Castrol Industrial North America, Inc.	24 months	Concentrates stable within a range of 40° F to 120° F; dilutions stable for approximately 90 days under laboratory conditions (though water hardness and evaporation may have an impact)
Master Chemical Corporation	12 months	Concentrates are stable within a range of 50° F to 90° F
Milacron Marketing Company	12 months	Products are stable in ambient temperatures

As the information in the matrix suggests, a good "rule of thumb" might be that concentrates kept at room temperature for up to a year will likely be in good shape for NTP's purposes.

Dilution

Soluble oil product concentrates, in contrast to other water-dilutable product classes (semisynthetics and synthetics), generally do not contain water in the product concentrate.[1] As a result, any change in product chemistry (including the possible reaction of water with other chemical components in the product concentrate) that might occur upon dilution would not occur if the soluble oil product concentrate were to be directly aspirated. Thus, in order to assure that laboratory animals are exposed to fluids representing conditions as close to possible to those of machinists, ILMA recommends that any soluble oil product be first diluted one part fluid concentrate to 20 parts deionized water before exposure.

Because other water-dilutable product classes already contain sufficient water to assure that any hydrolysis reactions would occur, ILMA believes that further dilution of such product classes is not necessary before exposure.

As we discussed at our meeting, research over the last 15 years strongly suggests that certain contaminates may play a major role in observed acute respiratory health effects. ILMA, therefore, believes that NTP should also consider exposing laboratory animals to dilutions of metalworking fluid products that are contaminated and compare those results to those of fresh dilutions. Such an inquiry would better simulate conditions in a metalworking shop.

[1] Byers, J. ed., *Metalworking Fluids*, at 165-189 in Marcel Dekker, New York, NY, 1994.

Product Formulations

The product formulas are trade secrets. None of the companies are therefore able to disclose product formulations *per* se through ILMA to NTP. During our meeting it appeared that NTP recognized this practical constraint. We would imagine also that NTP has an interest in independently determining the composition of the fluids.

Despite these limitations, ILMA is committed to balancing its offer of assistance to NTP with the need to protect this sensitive information from public disclosure. To this end, and because these products are complex and reverse engineering is difficult, we determined that providing a list of the chemical *categories* contained in each of the fluids might be a workable compromise. The matrix on Attachment 1 provides this information. The manufacturers of these fluids submitted these data voluntarily to ILMA with the understanding that this information would be handled on a confidential basis.

Attachment 1 is, in its entirety, exempt from disclosure under any Freedom of Information Act (FOIA) request. More specifically, Attachment 1 qualifies under the U.S. Department of Health and Human Services (HHS) FOIA regulation exemption for both trade secrets and confidential commercial or financial information, 45 CFR § 5.65.[2] ILMA respectfully requests that Attachment 1 be managed accordingly by NTP.

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[2] First, listing specific constituents of a manufactured product fits squarely within the regulatory definition of a trade secret:

> A trade secret is a secret, commercially valuable plan, formula, process, or device that is used for the making, preparing, compounding, or processing of trade commodities and that can be said to be the end product of either innovation or substantial effort. There must be a direct relationship between the trade secret and the productive process.

45 CFR § 5.65.1. These materials' status as "trade secrets" provides an independent basis for precluding disclosure in response to a FOIA request.

The materials' status as "commercial or financial information" provides a second, independent basis for precluding disclosure under a FOIA request. Under HHS regulations, "commercial information" must be withheld from a FOIA request to the extent that it was obtained "from a person" and that the commercial information is otherwise "privileged and confidential."

Component ingredients to a manufactured product satisfy the regulatory definition of commercial information: information that relates to "business, commerce, trade . . . [or] profits." 45 CFR § 5.65.2.1. ILMA is a private trade association, and thus these materials are submitted "from a person." *Id.* Finally, the information contained in these materials was compiled at the direction of counsel and thus satisfy the "privileged and confidential" requirement. *Id.*

As we understand the process, the National Institute for Occupational Safety and Health (NIOSH) identified the top ten marketers of metalworking fluids and selected, somewhat arbitrarily, five to six fluids from the top five marketers. The selected fluids were to represent a cross section of each marketer's line. From an initial list of 29 fluids, NTP determined that only 18 were commercially available to them.

NTP, through a contractor, chemically characterized the 18 available MWFs. NIOSH, using that information, along with available marketing materials, material safety data sheets, independent chemical analyses and the contractor's recommendations, narrowed the list to nine products for further evaluation by NTP. NIOSH, using an admittedly arbitrary process, selected three products from each of the three manufacturers whose products were commercially available. The products were sometimes chosen because they were representative of a category but also were sometimes chosen because they were complex or unusual.

Given this process, the fluids selected, while not in fact "top sellers" within their respective companies, do contain chemistries typical of more widely-used products. On the other hand, as each fluid is unique, ILMA believes testing results must be limited to that individual formulation. Indeed, as evidenced in Attachment 1, each of the soluble oil formulations contain chlorinated EP agents. Investigation results regarding the soluble oil fluids selected by NTP should not be applicable to non-additized soluble oils, which are more common in the industry.

ILMA thanks NTP for sharing information regarding its metalworking fluid selection process and looks forward to further information exchanges and discussion as testing and evaluation continues. ILMA would be pleased, for example, to review NTP's chemical analyses in an effort to help put the results into context. Indeed, to the extent the analytical results generated by NTP are inconsistent with what ILMA member companies know to be true, an opportunity to provide additional information to NTP may be in everyone's best interest.

Sincerely yours,

Celeste Powers

Celeste M. Powers, CAE
Executive Director

cc: SHERA Committee w/o Attachment 1 (via email)
Jeffrey L. Leiter, Esq.
Adam B. Cramer, Esq.