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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 Final Technical Report for TRIM® VX

Dear Dr. Xie:

The Independent Lubricant Manufacturers Association ("ILMA" or "Association") submits these follow-up comments on the National Toxicology Program's ("NTP") final technical report ("FTR") for the metalworking fluid ("MWF") TRIM® VX. The Association thanks NTP and the members of the Peer Review Panel ("Panel") for their diligent work and thoughtful dialogue during last month's Panel meeting. ILMA agrees with the Panel's instruction to NTP staff to include limiting language within the executive summary and elsewhere within the FTR that MWFs are inherently-unique, proprietary formulations and the results of NTP's study cannot be extrapolated and applied to other MWFs as a class. [1] Along with this proposed revision, ILMA respectfully requests that NTP make other revisions to the FTR for TRIM® VX that are outlined below.

The Chemical Characterizations of TRIM® VX Are Incomplete and Problematic

The chemical characterizations of the TRIM® VX samples were incomplete. While "reverse engineering" is admittedly technically challenging, [2] Master Chemical Corporation's comments showed that, of the 17 ingredients contained in the formula, NTP's analysis only identified 13 compounds and a hexane extractable material. Of those 13, only in eight instances were the identities of the compounds qualitatively correct. This raises concerns about what precisely NTP tested. Dr. Brock echoed this sentiment during the course of his oral comments at the Panel meeting (Recording Segment #61 – Time Market 11:09):

> **Dr. Brock:** And, indeed, the presentation here showed that there were some discrepancies between what was reported in Table 1 and what the manufacturer actually purports that the composition is. So ostensibly we don't know what was tested.

Further, there were issues of instability and likely stratification of TRIM® VX. Master Chemical advised its

[1] ILMA has been steadfast in its statement that MWFs are unique formulations and noted in its 2005 letter to Dr. Dan Morgan, "On the other hand, as each fluid is unique, ILMA believes testing results must be limited to that individual formulation."

[2] ILMA acknowledged this in its 2005 Letter to Dr. Dan Morgan.

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.

In addition, the lack of data presented regarding bacterial and fungal growth is particularly concerning. ILMA and Master Chemical requested the information in advance of the Panel meeting, but NTP denied these requests. During the course of the 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?
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> **Dr. Ryan:** That is correct
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> **Dr. Brock:** And did they?
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> **Dr. Ryan:** I believe they were stored at appropriate conditions
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> **Dr. Brock:** Appropriate conditions. But did they degrade over time?
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> **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.
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> **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. Further, Dr. Steven Florio of Master Chemical noted this in his oral presentation during the Panel meeting (Recording Segment #60 – Time Market 13:11):

> **Dr. Florio:** Noting also that it was compared to a five-degree Celsius sample, anyone that has ever used an emulsion would understand that you do not store emulsions at low temperature. They don't hold together. They're not meant to be operated at five degrees. So I would question whether or not that represented an adequate control.

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.

NTP's Highest Dose Level Was Inappropriately Selected

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/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/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. NTP might have anticipated this possibility on the basis of the three-month studies and considered that possibility in the selection of 100 mg/m^3 as the high dose. NTP should address whether the possibility of a non-genotoxic mechanism played a role in the selection of the doses and also how it views that possibility in light of the results from the two-year studies.

NTP must provide further clarification in its FTR for TRIM® VX that adequately explains why the 100 mg/m^3 dose level was selected. 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 basd 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.
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> 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 Dr. Brock's comments elicited highlighted 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.

ILMA similarly shares Dr. Brock's concern regarding the highest dose level chosen for the study. NTP must provide a sufficient scientific justification for the dose level of 100 mg/m^3 other than it provided an easier basis for comparison to previous studies undertaken by NTP.

NTP Must Clarify Its Use of "Good Laboratory Practices"

The foreword of the draft technical report for TRIM® VX notes, "[t]he NTP conducts its studies in compliance with its laboratory health and safety guidelines and FDA Good Laboratory Practice ("GLP") Regulations and must meet or exceed all applicable federal, state, and local health and safety regulations." ILMA is concerned with the manner in which several portions of the study were conducted as outlined above. Further, Dr. Brock articulated the following issues during his oral comments at the Panel meeting (Recording Segment #61 – Time Marker 11:27):

> **Dr. Brock:** As a study being conducted by GLPs, it is imperative that the composition of a compound be well characterized under GLPs. And frankly I don't think that has been well handled here.
>
> This gets to some of the discussion around stability. Only one lot number was used in the two-year study. Was this stable over the duration of the study? This information presented in this paragraph suggests periodic analyses was conducted consistent with GLPs. However, no reference to these data are cited. Where are the methods? What were the methods used to test the stability of the test article and aerosol chamber concentrations? Were they validated? This should be stated. The authors also should cite the appropriate appendix, aerosol generation, where the results are.
>
> And I would even, as my question during your presentation alluded to, it's really unclear in the report what the comparisons were made to the frozen samples. And I make note of the presentation here about that. Comparisons and whether or not that frozen sample was really stable over the duration of this study. It wasn't frozen it was refrigerated actually, I understand.

Given the concerns addressed by ILMA in several written submissions, in the Association's oral comments during the Panel meeting, and Dr. Brock's remarks during the Panel meeting, NTP should clarify in its FTR how it closely followed all applicable GLP guidelines.

TRIM® VX Is a Unique Formulation

As discussed at length in ILMA's written and oral comments and during the course of the Panel meeting, TRIM® VX is a unique MWF. The National Institute for Occupational Safety and Health ("NIOSH") and NTP's selection process supports this contention. Additionally, ILMA understands that TRIM® VX was considered "unique" by NTP even from among the MWFs evaluated.

Further, during the course of the Panel meeting, Dr. Brock and Dr. Mirsalis acknowledged the unique properties of TRIM® VX that preclude extrapolation of the results to other MWFs (Recording Segment #64 – Time Marker 13:13):

> **Dr. Mirsalis:** You know, much has been made about the selection of whether this was representative. And, I mean, I think in response to those who made some of the public comments, at the time it seemed like a good idea . . . I do think in the introduction you probably should make that point that, you know, it's an example. It was picked at the time, it is relatively small-volume use, you know, and has been discontinued. ***I mean, I think it is important point to put context on*** [emphasis added].

Dr. Brock echoed Dr. Mirsalis' arguments (Recording Segment #64 – Time Marker 14:25):

> **Dr. Brock:** But you are absolutely correct, ***these materials are not representative because of the complexity of this field, they are individual materials*** [emphasis added]. And they will be discussed in that way in these reports. And we appreciate the encouragement to continue down that vein.

[3] For a more detailed discussion of NOISH and NTP's selection process, see ILMA's written submission from February 2, 2016 and ILMA's oral comments presented on February 16, 2016 at the Panel meeting.

OSHA's HCS 2012 Precludes Extrapolation of the Conclusions to Other MWFs

The Occupational Safety and Health Administration's ("OSHA") Hazard Communication Standard 2012 ("HCS 2012") Appendix A.6 provides rules for dealing with the carcinogenicity of mixtures. It states that the results of a positive carcinogenic study of a mixture cannot be extended to other mixtures, unless there are data on individual ingredients and a plausible mechanism. More specifically, Appendix A.6.3.2 states:

> A mixture may be classified based upon 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.

Further, Appendix A.6.3.3 discusses the "bridging principles" when data are not available for the complete mixture excerpted below:

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

As a result, ILMA concludes that any testing results from TRIM® VX cannot be extended to other MWFs, individually or as a class, unless the compositions of the other MWFs are so similar and there are sufficient data on both the individual ingredients and similar tested mixtures so as to allow application of "bridging principles" as described in 20 CFR 1900.1200, Appendix A.6.3.2 and A.6.3.3.

Conclusion

ILMA appreciates this opportunity to provide these follow-up comments regarding NTP's FTR for TRIM® VX. ILMA firmly agrees with the above-outlined statements from Drs. Mirsalis and Brock that "these materials are not representative" and the conclusions cannot be applied to any other MWF.

Sincerely,

Holly Alfano
Chief Executive Officer

cc: ILMA Board of Directors
ILMA SHERA & MWF Committee
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Jeffrey L. Leiter, Esq.
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