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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 concerns¹.” 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.

President, Beth Ann Jones, Hangsterfer’s Laboratories, Inc.
Vice President, Dave Croghan, Maxum Petroleum
Treasurer, Barbara Kudis, Allegheny Petroleum Products Company
Secretary, Chuck Decker, American Oil & Supply International LLC

Immediate Past President, Frank H Hamilton III,
South Atlantic Services, Inc.
Chief Executive Officer, Holly Alfano
General Counsel, Jeffrey L. Leiter

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" section² nor the "Chemical Characterization and Generation of Chamber Concentration" section³ 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 setting⁴. [Emphasis added.]

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

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/m³, 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/m³ 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 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.

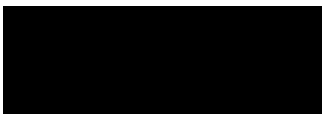
Application of these principles found in Appendix 6, Carcinogenicity, to other MWFs means that there cannot be an extension of the results to other MWFs unless other similarly composed MWFs also are found to show evidence of carcinogenicity and that there is found “sufficient data on...the individual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