Master Chemical Corporation
501 West Boundary
Perrysburg, OH 43551-1200 USA
Tel: 419-874-7902
www.masterchemical.com

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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:

Master Chemical Corporation ("MCC") submits these follow-up comments on the National Toxicology Program's ("NTP") final technical report ("FTR") for the metalworking fluid ("MWF") TRIM® VX ("VX"). As you know, MCC was the manufacturer of VX.

MCC thanks NTP and the members of the Peer Review Panel ("Panel") for the hard work and insightful discussion at the February 16, 2016 Panel meeting. MCC submits the following comments by the topics set forth below.

Limitations on the Treatment of VX as being "Representative" of Soluble MWFs

At the conclusion of the Panel discussion and prior to the vote on the Panel findings, the Panel Chair, Dr. Jon Mirsalis, with input from Dr. John Bucher, Associate Director NTP, summarized the selection of VX as a test product and gave instruction to NTP staff to include limiting language within the executive summary and elsewhere within the FTR. The essence of these instructions was to note that MWFs are inherently-unique, complex, proprietary formulations and the results of NTP's VX Study cannot be extended in a "top down" manner to reach toxicity conclusions about other soluble MWFs as a sub-class of MWFs or generally to the universe of MWFs. This discussion is found at NTP Recording Segment #64 - Time Marker 13:06 and reads as follows:

> DR. MIRSALIS: Are there other comments from the panel? If not, I have a couple comments.
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> You know, much has been made about the selection of whether this [VX] was representative. And I think in response to those who made some of the public comments, at the time it seemed like a good idea, you know, and that was probably

a decade ago. Just as when I bought AOL stock in 1998, it seemed like a good idea at the time.

The fact that it turns out that it's small volume, it's been discontinued, it is what it is after a decade. 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 now been discontinued. I mean, I think that is an important point to put context on. But I know there's concern that, you know, NTP is going to draw conclusions about all metal working fluids. I mean, and John Bucher may comment. I don't think that's within NTP's purview. We put the data out, this is the study, it stands alone. Others may draw whatever conclusions they choose to draw. But, I mean, NTP is not going to come out with a statement saying, well, based on this all soluble metal working fluids, you know, have these properties. And, John, do you want to either confirm or refute that?

DR. BUCHER: No, I would confirm that. And I would just say that you have some idea from the discussions today how difficult it was to just sort through all of the different products out there and try to understand what the identifiable components were versus the trade secret components, and try to come up with a selection of materials to test in two-year studies that would give some indication of whether some of the things that we're seeing in the metal working fluids industry could be attributed to materials that were not contaminated with bacteria that happens normally during the process of their use.

So these two materials, the Cimstar and the Trim VX, were selected after a very long and arduous selection process with lots of pre-chronic information generated on a lot of these.

But you are absolutely correct, these materials are not representative because of the complexity of this field; they are individual materials. And they will be discussed in that way in these reports. And we appreciate the encouragement to continue down that vein.

DR. MIRSALIS: Okay. And my last comment was, you know, again, much has been made of the chemistry. And I know the statement was made, earlier we heard NTP didn't provide the reports. I think just right now it's an availability issue during the peer-review process. I think, and I would encourage, that information should be included in the final report, you know, the chemical methods used, the analysis. I mean, I know that they exist and they're available, they're not secret. I think those should be included.

MCC requests that these changes, including those noted by Dr. Bucher, be included in the FTR. MCC also specifically requests that all of the supporting data whether previously requested by MCC, requested by ILMA, referred to in the preliminary Report, mentioned

by NTP Presenters, mentioned by any of the Panel members, or mentioned in Dr. Mirsalis' comments be included in the FTR and its appendices.

VX Stability and "Good Laboratory Practices"

MCC raised in its written comments and in its oral presentations critical concerns about the stability of its VX product as tested by NTP. These concerns are even more problematic in light of the details of NTP's handling of the VX Product during the Study period and which were first revealed during the peer review presentation, and NTP's broad (but unsupported) assertion that the NTP Study was conducted in compliance with FDA Good Laboratory Practices.

Relative to these concerns, MCC has previously provided the Panel with a copy of a letter dated October 21, 2005 from the Independent Lubricant Manufacturers Association ("ILMA") to Dr. Daniel L Morgan of NIEHS. (An additional copy of the letter is attached to these comments as Exhibit A for your convenience and is hereinafter referred to as the "ILMA Letter".) The ILMA Letter, based on its clearly stated terms, was submitted to Dr. Morgan in furtherance of the planning for the MWFs Studies to be undertaken by NTP including this specific study of Trim VX. The ILMA Letter is a follow up to "in person" staff meetings between NTP and ILMA and to memorialize the agreement for a "mutual exchange of information" between NTP and ILMA. Thus, NTP had actual notice of the information contained in the ILMA Letter well in advance of the animal testing that was conducted for this study. NTP has never suggested that it was not aware of this information.

The ILMA Letter advised NIEHS and (through Dr. Morgan) NTP of two pieces of information which are critical and highly relevant to the VX Product stability issue.

1. The first is that the VX Product has a "Shelf Life" or "expiration date" of just 12 months following manufacture.
2. The second is the temperature range within which VX remains stable: "Concentrates [of VX] are stable within a range of 50° to 90° F" (50°F converts to approximately 10°C).

NTP asserts without supporting documentation that this Study of Trim VX was performed "in compliance with its laboratory health and safety guidelines and FDA Good Laboratory Practices ("GLP") Regulations". (Emphasis added. See Study Foreword and Quality Assurance Methods, page 47.). MCC still maintains that using a test product in this study beyond its published expiration date is simply NOT consistent with any FDA procedures and certainly not with FDA's GLP.

It is axiomatic that the FDA has worked tirelessly for decades in trying to convince manufacturers to state shelf life or "expiration dates" for the foods, drugs, cosmetics, health care devices and other products which FDA regulates. It has made a similar effort

to educate consumers to pay attention to those expiration dates and to not use regulated products beyond each product's published expiration date. Today, the FDA continues its efforts through public service announcements, social media and other outlets to convince consumers that they should NOT use drugs and other products beyond their published "expiration dates". (See "Expiration Dates Matter", http://www.fda.gov/forconsumers/consumerupdates/ucm251658.htm in which an FDA Pharmacist warns, "If your medicine has expired, its chemical composition may have changed… If your medicine has expired, don't use it.") NTP perhaps missed this announcement. None the less, to suggest that the NTP's use of expired VX product in this toxicology test complies with FDA's Good Laboratory Practices is at best misleading and inaccurate.

This concern was raised by Dr. Brock in his comments about the VX Product stability and specifically in the context of the FDA GLPs. His comments are found in several sections, the first, immediately following the conclusion of Dr. Ryan's Presentation are found at NTP Recording Segment #59 - Time Marker 20:13 and read as follows:

> DR. BROCK: I'm a little confused by the stability assessments that were done on the test article. Can you go back to that slide? It's like the third or fourth slide or something like that?
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> DR. RYAN: Yeah, I think I can. Sorry, bear with me here. I can do my best. But I also have here our chemist and toxicologist here that are probably better to answer this.
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> DR. BROCK: I think you went past.
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> DR. RYAN: This one? Sure. [This is Dr. Ryan's Presentation Slide 9 which is attached as Exhibit B.]
>
> DR. BROCK: All right. So you did stability assessment on the test article?
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> DR. RYAN: Uh-huh.
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> DR. BROCK: During this. And then the last item here, data compared to frozen reference sample?
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> DR. RYAN: Uh-huh.
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> DR. BROCK: So, in other words, you did the stability real-time with the unfrozen material but compared it to the frozen sample. Do I understand that correctly?
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> DR. RYAN: Yes. So when we receive the test material in, the time of

receipt, we take aliquots out and freeze that, 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 your 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. [The NTP Study Chemist corrected Dr. Ryan and advised the Panel that the aliquots taken from the bulk sample were stored above freezing at 5° C.]

This exchange actually raised more troubling questions than it answered. NTP revealed for the first time that its "solution" to the wholly improper use of the VX Product for testing beyond its expiration date, was to place samples of the VX Product into cold storage and use those near frozen samples later as "controls" against which the aging room temperature bulk storage VX Product was measured, over time, for degradation. (See Slide 9 from the presentation (Exhibit B) which explains this process.)

The problem is that this "solution" assumes that storing VX Product aliquots at a point near freezing would "preserve" the VX Product aliquots and stop the VX Product aliquots from becoming unstable and degrading: That the near frozen storage would preserve a "stable" control sample against which the aging VX bulk Product could later be measured. This underlying incorrect assumption is the exact issue which Dr. Brock is getting at in his questions. We know the assumption is incorrect because MCC published information and the ILMA Letter specifically advised NTP in advance of the Study that the assumption was not correct:

"Concentrates [of VX] are stable within a range of 50° to 90°F" (see Exhibit A, page 2).

50°F (the stated low end of VX Product stability) converts to 10°C. The aliquots were stored at 5°C. Inexplicably, without further analysis, without testing or examining its assumption, NTP ignored the specific stability information which was provided to it by MCC through the ILMA Letter and built its Study method on this false assumption. In fact, based on the information contained in the ILMA Letter, NTP should have assumed that the storage of the aliquots at 5°C actually would cause the VX Product aliquots to become unstable and to degrade. NTP had no information (and still has no information) contrary to MCC's specific VX Product information on this point.

To make the problem clear (using a food analogy) think of a familiar emulsion like the food product "Sour Cream". If you freeze Sour Cream, the material becomes unstable and degrades: The emulsion breaks down, ice crystals form, chemical changes occur and the product, as it thaws, separates into individual components with fluids, solids, and lumps of curds replacing the formerly stable and homogeneous substance. Even if re-mixed or "stirred" after thawing, Sour Cream does not re- homogenize and the texture remains lumpy and inconsistent. Similarly, if you store Sour Cream beyond its expiration date, you will also observe the material becoming unstable as it degrades: The emulsion breaks down, chemical changes occur and the product, as it degrades, separates into individual components with solids, fluids, and lumps replacing the formerly stable and homogeneous substance. The FDA, operating under its GLPs would not use the expired, unstable degraded or the frozen Sour Cream in a test intended to determine the safety, purity, nutritional effects, or health impact of fresh Sour Cream.

Dr. Brock came back to this exact point in his follow-up comments later in the Panel discussion. This part of his comments are found at NTP Recording Segment #61 - Time Marker 10:47 and read as follows:

> DR. BROCK: I'm discouraged by the fact that the compound was received from Master Chemical and yet the composition was not provided to NTP. And, indeed, the presentations 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 in this.
>
> 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's been well-handled here.

Dr. Brock returned to this again in further comments a few minutes later. These are found at NTP Recording Segment #61 - Time Marker 15:22 and read as follows:

> DR. BROCK: Materials and methods. 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 analysis 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 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.

Of course, Dr. Brock is noting that none of the stability analysis methodology or data has been disclosed by NTP. This is the same information which was requested by MCC and by ILMA and which NTP has declined to provide. He is also observing that, on a more general basis, the NTP claims of GLP compliance are not supported by the information presented. MCC agrees that this support information must be provided as part of the FTR.

MCC would like to reaffirm one additional point from its written comments in light of the information provided by NTP as part of the Peer Review session. At page 3 of its prior written comments, MCC made the following observation while quoting the Table 1 of the NTP Draft report:

> The most that the Study can state is that, "The composition of both lots of Tested Product was <u>similar</u> based on analysis (Table 1) (page 34)."

As pointed out by MCC, it appears that the most that could be said about the testing of VX Product stability as it aged over time (and specifically as it passed its expiration date) is that the "before aging" and "after aging" materials were "SIMILAR". If so, those test results by themselves certainly did not demonstrate that the VX Product had not become unstable or degraded over the course of the Study. Had there been no degradation or instability, and if the same rigorous tests were performed, the "before aging" and "after aging" results should have been "identical", "the same", "virtually the same" or at worst "substantially the same". Prior to the Panel presentation, giving NTP the benefit of the doubt, one might have concluded that the use of the word "SIMILAR" was merely an inaccurate slip which perhaps understated the results of the analysis.

However, based on the Panel discussion, we now know that it was not an inadvertent understatement by NTP. Rather, it was a carefully chosen word which put the stability analysis test results in their best light. We know this because Dr. Ryan called upon the Study Chemist to explain the stability analysis procedures. While the name of the Chemist is inaudible on the NTP recordings (her microphone had not yet been turned on when she gave her name) her statement is clear on the recording. Her comments and exchange with Dr. Brock immediately follows, and is a continuation of, the first above

quoted remarks of Dr. Brock and are found at NTP Recording Segment #59 - Time Marker 22:04 and read as follows:

> DR. BROCK: So you did the frozen sample stability over the duration of the study as well?
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> DR. RYAN: I believe so. Do you want to comment on that, Dr. – [referring to the NTP Chemist]
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> NTP CHEMIST: (Inaudible)…. NTP. I just want to clarify one thing, one editorial. It's not a frozen reference. The sample was stored at five degrees in the refrigerator. So what we compared when we first got to test material within a month we analyzed for the panel but we just didn't show it. What we did was we compared that data over time to samples taken at different times before testing, during testing, and after testing, and then compared the values to the original bulk material.
>
> DR. BROCK: Okay. It's a little confusing in the report.
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> DR. RYAN: And we understand that and we can take some steps to clarify that.
>
> NTP CHEMIST: I can clarify that. In the report the initial information given is for the bulk test material. And then we have a paragraph saying that the data that we did during the testing is <u>similar</u>. But, yes, you're right, we did not give specific data, but by comparison we confirmed that it is <u>similar</u> (emphasis added).

So, (i) being aware of the concerns raised in MCC's written comments relating to the use of the inconclusive word "SIMILAR", (ii) after participating in an open exchange with Dr. Brock about his concerns about this exact same stability analysis issue, and (iii) after stating that her comments on the record were being offered to "clarify" the product stability analysis, the NTP Study Chemist again, in two separate instances, continued to use the same inconclusive terminology: "SIMILAR". As noted, she could only say, "we did not give specific data, but by comparison we confirmed that it [the post expiration VX Product and the cold stored VX Product] is <u>similar</u>."

Returning to the food analogy briefly, MCC submits that if one were to conduct a chemical analysis comparing (i) the frozen and thawed Sour Cream with (ii) the post expiration date Sour Cream, you would almost certainly conclude that the 2 materials were "SIMILAR". In fact, if you conducted a chemical analysis comparing (i) fresh Sour Cream with (ii) the post expiration date Sour Cream, you would still almost certainly conclude that the 2 materials were "SIMILAR". However, in neither case would the findings be that the two test materials were the "same" or "identical", but they would be "SIMILAR". The FDA would not use post expiration date, separated or degraded Sour

Cream in a study designed to test the safety, nutrition or other properties of fresh Sour Cream.

This remains the fundamental flaw in the VX Study which regrettably cannot be corrected after the fact by simply by claiming that the Study complied with FDA GLP. As noted in MCC's original written comments to the draft Report, when comparing (i) the NTP Chemical analysis of the VX Product as set forth in Table 1 of the draft Report (at page 34), (ii) the NTP findings that the products were only "similar", and (iii) the actual formulation of a fresh batch of VX Product, the resulting chemical discrepancies are only consistent with the conclusion that the VX Product in bulk storage became unstable and degraded during the Study period. This conclusion specifically and simply explains why some, but not all of the actual components were among the "measured" components and why among the majority of the "measured" components which were actual components, the concentration of the "measured" components were so different from the fresh VX formula concentrations (as much as 88% off in some cases). NTP's unsubstantiated alternative conclusion is that "SIMILAR" is close enough and that the discrepancies are the result of inaccuracies in the rigorous reverse engineering analysis conducted by NTP. Apart from completely ignoring any consideration of the possible application of Occam's razor to this question, if the reverse engineering analysis was so crude, why did NTP in Table 1 report its results out to two decimal points, what additional components were not "measured" through this analysis, and why did NTP bother with this expensive analysis if its results are so inaccurate and unreliable?

With regard to these issues, MCC submits that the FTR should strike all references claiming that this Study was conducted in compliance with the FDA GLP standards. Beyond this the FTR should state affirmatively that one conclusion (if not the most likely conclusion) of the NTP chemical analysis of the VX Product, which was undisputedly used past its expiration date, was itself very likely degraded and separated during at least some portion of the time during which the test animals were exposed. This conclusion is entirely consistent with what has been revealed to date by the NTP. It should be noted that a stronger affirmative statement on this subject may be necessary when the full supporting data is released by NTP consistent with the instructions of Dr. Mirsalis in his closing remarks discussed above. MCC reserves the right to make additional comments when this information (which was previously requested) is eventually released.

ILMA's Comments on the FTR

In addition to the comments made and issues specifically addressed herein MCC joins in the comments on the FTR which are being submitted by separately by the Independent Lubricant Manufacturers Association. MCC has reviewed these separate comments and endorses and adopts both the comments and the recommendations made by ILMA regarding the Final Technical Report.

/S/ Steven M. Florio

Steven M. Florio, PhD
Chief Technology Officer

Master Chemical Corporation
501 West Boundary
Perrysburg, Ohio 43551-1200

Attachments:

Exhibit A: ILMA Letter
Exhibit B: Slide 9 NTP Presentation