UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MAY 11 2000

OFFICE OF
AIR AND RADIATION

Donald R. Lynam, Ph.D., CIH, P.E.
Vice President, Air Conservation
Ethyl Corporation
330 South Fourth Street
Richmond, VA 23219-4304

Dear Dr. Lynam:

On January 25, 1999, the Environmental Protection Agency (EPA) notified you of a proposed test program requiring emission and health effects testing for the gasoline additive methylcyclopentadienyl manganese tricarbonyl (MMT), in accordance with the Alternative Tier 2 provision of the fuels and fuel additives (F/FA) health effects testing regulations.[1] A Federal Register notice[2] established a 60-day public comment period allowing interested parties to comment on the proposed requirements. This letter and its attachments notify you that EPA has adopted final test requirements pursuant to its January 25, 1999 proposal. This notice is directed to you specifically in your capacity as the responsible administrative officer of Ethyl Corporation in this matter. EPA has previously stated its understanding that Ethyl has agreed to assume the responsibility for coordinating any Alternative Tier 2 testing requirements with other potentially responsible parties, specifically registrants of unleaded gasoline products who have amended (or will amend) their composition statements to permit use of MMT in their products.[3]

The Alternative Tier 2 testing regimen adopted today is being required pursuant to sections 211(b)(2) and 211(e) of the Clean Air Act. It is designed to assist EPA in identifying and evaluating the adverse effects on human health, if any, of fuels containing up to 1/32 gram per gallon (gpg) manganese (Mn) in the form of MMT and in determining whether there is any need for future regulatory action pursuant to Section 211 of the Act. The Alternative Tier 2 program includes some types of testing not

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[1] The F/FA health effects testing program regulations are codified at 40 CFR part 79, subpart F. The Alternative Tier 2 provisions appear at 40 C.F.R. § 79.58(c).

[2] Proposed Alternative Tier 2 Requirements for Methylcyclopentadienyl Manganese Tricarbonyl (MMT), 64 FR 6294, (February 9, 1999).

[3] See the November 9, 1995 letter from EPA Counsel, Tim Backstrom, to Ethyl Counsel, F. William Brownell. (See EPA Air Docket #A-98-35, III-B-2).

ordinarily included in standard Tier 2. Further Alternative Tier 2 testing for MMT may ultimately encompass more definitive testing related to some standard Tier 2 health effect endpoints, and include some other types of data not ordinarily included in standard Tier 2.[4] EPA has also determined that it will construe the completion and submission by Ethyl of all tests required by this notification letter as satisfying any Standard Tier 2 testing requirements that might otherwise apply with respect to the fuel and fuel additive group for MMT.

In finalizing the Alternative Tier 2 testing requirements for MMT described below, EPA has identified particular instances in which testing protocols should be submitted to EPA for review and approval prior to commencement of testing. In addition, EPA believes that the development of testing protocols will be enhanced by inclusion of a peer review process and will generally require that such a process be followed, as explained under the section Study Protocols, and in Attachment A.

EPA has concluded that a testing regimen which modifies the standard screening requirements of Tiers 1 and 2 is necessary and appropriate for this F/FA group. As you know, EPA has had ongoing consultations with Ethyl and its contractors, other interested parties such as the Environmental Defense Fund (EDF, now known as Environmental Defense), and scientists with special knowledge of the potential effects of inhaled manganese concerning testing needs and priorities. Based on these discussions, EPA scientists have identified specific research needs related to assessment of the potential risks associated with use of fuels containing MMT. In general, EPA has concluded that it is appropriate to address most of these research needs under the Alternative Tier 2 provisions,[5] rather than waiting for the completion of standard Tier 2 and then developing follow-up test requirements at the Tier 3 level.[6] By proceeding with Alternative Tier 2 testing, EPA believes that all needed data can be obtained over a shorter period of time and at lower overall cost.

As proposed in the January 25, 1999, notification and finalized below, the Alternative Tier 2 testing requirements adopted by this letter are intended to be the first stage in a two-stage Alternative Tier 2 test program. Today's action finalizes the testing to be required during the first stage of the Alternative Tier 2 testing for MMT.

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[4] See Fuels and Fuel Additives Registration Regulations, 59 FR 33042, 33081 (June 27, 1994) (discussing appropriate use of the Alternative Tier 2 requirements).

[5] Our intent to require special testing under the Alternative Tier 2 was previously communicated to you in a November 28, 1994 letter from EPA Counsel, Tim Backstrom, to Ethyl Counsel, F. William Brownell. (See EPA Air Docket #A-98-35, III-B-1).

[6] As EPA stated in promulgating the F/FA registration regulations, use of the alternative Tier 2 provisions "can facilitate earlier and potentially more efficient acquisition of the required data" than use of standard Tier 2 testing and subsequent Tier 3 testing. 59 Fed. Reg. at 33081.

EPA will notify you separately of any additional Alternative Tier 2 testing to be included in the second stage, and will afford you a separate opportunity to comment on such testing when it is proposed. EPA intends to evaluate the results produced in the first stage of testing, as well as any other information which may be submitted to or obtained by EPA in the meantime, in determining the specific nature and scope of any second stage of Alternative Tier 2 testing.

The testing requirements adopted by this notification are intended in part to assist EPA in defining the atmosphere to be employed for each test, and in resolving other issues, with respect to neurotoxicity testing and other testing requirements EPA may decide to propose as Alternative Tier 2 tests in the future. EPA has determined that it will not impose, or attempt to impose, any additional testing requirements for MMT, beyond those set forth in this letter, before EPA selects an appropriate atmosphere and design parameters for each additional Alternative Tier 2 test it may propose. EPA has further determined that it will not under any circumstances impose, or attempt to impose, additional emission characterization testing requirements for MMT beyond those specified in this letter.

While the necessity for and specific elements of the second stage of Alternative Tier 2 testing will be determined later, EPA scientists currently anticipate that this second stage may include longer term neurotoxicity and other toxicology testing in the general categories that EPA and Ethyl have been discussing for some time. The two-stage approach to Alternative Tier 2 testing will allow the collection during the first stage of data on pharmacokinetics and emissions characterization which are intended to assist EPA and Ethyl contractors in making appropriate decisions concerning the design of those toxicology studies which EPA may propose for inclusion in the second stage. For example, this testing may help identify appropriate manganese compounds and dose levels for longer term animal toxicology studies.

The specific study requirements that EPA has adopted in the first stage of Alternative Tier 2 testing for MMT are set forth in the attachments. General requirements which would be applicable to all testing are described in Attachment A, inhalation pharmacokinetic studies are described in Attachment B, emission characterization studies are described in Attachment C, and the schedule for completion of all testing required pursuant to this notification is set forth in Attachment D. The remainder of this letter explains why EPA has concluded that the Alternative Tier 2 testing program is necessary, describes the overall structure of the test regimen, describes the general nature of the requirements, discusses the peer review process for developing study protocols, discusses future Alternative Tier 2 testing that the Agency envisions, and reviews the administrative aspects of the Alternative Tier 2 process. This letter also describes the comments received concerning the January 25, 1999 proposal, summarizes the EPA response to those

comments, and describes those changes in the proposed testing requirements that EPA decided to make in response to the comments.

The Necessity for the Alternative Tier 2 Testing Program

In 1990, the EPA Office of Research and Development (ORD) assessed the potential health risks associated with the use of methylcyclopentadienyl manganese tricarbonyl (MMT) as an additive in unleaded gasoline.[7] Later, ORD reaffirmed its assessment[8] after considering a resubmitted Clean Air Act section 211(f)(4) fuel waiver application for MMT from Ethyl Corporation. These evaluations identified as a key health issue associated with the use of MMT as a fuel additive the potential health risk associated with inhalation exposure to manganese particulates resulting from the combustion of MMT in gasoline. A new assessment of the risks associated with MMT use was presented in a revised risk assessment in 1994 and confirmed these concerns.[9] These evaluations concluded that:

> ...it is impossible to state whether projected population exposures would lie above or below a presumed threshold level on the actual concentration-response curve for Mn neurotoxicity. This gap between expected exposure levels and the lowest concentrations obtained by modeling the concentration-response relationship (at least, by the quantal linear model) makes it impossible to make any assertion regarding the likelihood of a health risk at projected exposure levels. However, this conclusion should not be interpreted to imply that, therefore, no health risk is expected to exist at exposure levels exceeding the inhalation reference concentration (RfC).[10]

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[7] U.S. Environmental Protection Agency. (1990) Comments on the use of methylcyclopentadienyl manganese tricarbonyl in unleaded gasoline. Washington, DC: Office of Research and Development.

[8] Preuss, P.W. (1991) ORD's Comments on Ethyl Corporation's July 12, 1991, Resubmittal of a Waiver Application for Use of Methylcyclopentadienyl Manganese Tricarbonyl (MMT) in Unleaded Gasoline (Memoradum to Richard Wilson). Washington, DC: U.S. Environmental Protection Agency, Office of Research and Development; December 12, 1991.

[9] U.S. Environmental Protection Agency. (1994) ORD's "Reevaluation of Inhalation Health Risks Associated with Methylcyclopentadienyl Manganese Tricarbonyl (MMT) in Gasoline, July 1, 1994" Washington, DC: Office of Research and Development.

[10] An Inhalation Reference Concentration (RfC) is defined as an estimate (with uncertainty spanning about an order of magnitude) of a continuous inhalation exposure level for the human population (including sensitive sub-populations) that is likely to be without appreciable risk of deleterious non-cancer effects during a lifetime.

As a result of its risk evaluations, EPA concluded in 1994 that "to more accurately define an RfC for manganese and to more accurately predict the distribution of expected manganese exposures associated with MMT use, additional research will have to be completed."[11] At that time, EPA's Office of Research and Development prepared a report identifying research which would allow a more accurate evaluation of the risk involved in utilizing MMT in unleaded gasoline.[12] Some of the research described in this ORD report is intended to address toxicological endpoints which are also addressed by standard Tier 2 tests[13], while other research described in the report is intended to address other endpoints, and to assist in characterizing potential manganese exposures associated with use of MMT. In addition to the types of research discussed in the ORD report, it has become apparent that it would be constructive to study certain pharmacokinetic and emission characterization issues further before proposing additional test requirements. This notification announces that EPA has adopted specific testing requirements in each of these areas, as described in detail in the attachments, as part of the first stage of Alternative Tier 2 testing.

A Two-Stage Approach

As explained above, EPA scientists previously concluded that significant toxicology testing in animals would be necessary to properly evaluate the potential health risks presented by use of MMT in fuels. Further, at the present time it is the view of EPA scientists that adequate animal testing will ultimately require testing in non-human primates. Unless it can be clearly demonstrated that an alternative route of exposure would be equivalent to inhalation exposure, each such animal test will require the generation of an experimentally controlled atmosphere containing one or more manganese compounds. The Agency believes that the composition of this atmosphere may be an important element in using such testing to characterize potential human risks associated with MMT use. For example, it is well known that certain species of manganese are highly soluble and other species are not. Thus, depending on the species of manganese inhaled, more or less manganese may be absorbed into the blood. In addition, EPA has previously suggested that differences in the valence state

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[11] See 59 FR 4227, August 17, 1994.

[12] ORD originally reviewed the information needed to improve the risk characterization in: Preuss, P.W. (1991) ORD Document on Information Needed to Improve the Risk Characterization of Manganese Tetraoxide (Mn_3O_4) and Methylcyclopentadienyl Manganese Tricarbonyl, December 12, 1991 [memorandum to Richard Wilson]. Washington, D.C: Environmental Protection Agency, Office of Research and Development, December 16, 1991. For further information the reader is referred to Air Docket A-93-26, II-A-16. ORD reevaluated these information needs in light of new information. See memo from Peter W. Preuss to Richard Wilson dated July 13, 1994, Docket A-93-26, II-A-18.

[13] For example, it is clear that the standard Tier 2 neurotoxicity will not address adequately the potential neurotoxicity of inhaled manganese to humans because of differences in susceptibility due to age, species, etc.

of inhaled manganese may result in differences in distribution or toxicity.[14] In order to assure that the atmosphere used in each such animal test is properly selected, EPA believes that it is important to determine the composition of actual manganese particles emitted by vehicles burning fuels containing MMT.

At this time, Ethyl Corporation has completed a substantial amount of exhaust speciation work, composed of work performed for its Tier 1 submission under the F/FA health testing regulations as well as additional work Ethyl has performed on its own initiative.[15] Although the work performed to date has contributed significantly to our understanding of the composition of manganese particles in exhaust, EPA has nonetheless concluded that there are important unresolved questions regarding the relative proportions of the various manganese species present in vehicle exhaust. For example, although Ethyl concludes in its submission that "manganese from the use of MMT is emitted primarily as manganese phosphate"[16], it appears that in some cases, the amount of phosphorous needed to produce the manganese phosphate may not be available in sufficient concentrations from potential phosphorus sources (i.e., the crankcase oil). Furthermore, the Ethyl report clearly shows that other manganese species, i.e., manganese oxides and manganese sulfates, are likely present. Moreover, the Agency believes it would be helpful to evaluate whether various untested driving scenarios (e.g., other vehicle types and other driving cycles more representative of urban driving), result in significant differences in the proportional contribution to total manganese of manganese species other than manganese phosphate.

Pharmacokinetic (PK) studies, specifically the development of a physiologically-based pharmacokinetic (PBPK) model, may also shed light on the appropriate atmosphere to choose for each test, as well as other issues pertaining to the design of animal testing. For example, PK studies may provide insight into which species of manganese are most problematic in terms of delivery to the brain, thus providing some information indicating if the precise mix of species in the testing atmosphere is even important or, alternatively, a PBPK model might help define a "worst-case" atmosphere. Moreover, a PBPK model may help define dosage levels and other parameters which would be utilized in designing a long-term animal toxicology test program.

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[14] U.S. Environmental Protection Agency. (1994) ORD's "Reevaluation of Inhalation Health Risks Associated with Methylcyclopentadienyl Manganese Tricarbonyl (MMT) in Gasoline, July 1, 1994" Washington, DC: Office of Research and Development.

[15] "Characterization of Manganese Particulates from Vehicles using MMT Fuel", Ethyl Corporation. Contributions from Lawrence Livermore National Laboroatory, Southwest Research Institute, University of Minnesota, Research Triangle Institute, and Ethyl Research and Development. September 10, 1997.

[16] Ibid p.1, Executive Summary.

Health Studies

The Agency is adopting health study requirements, as described in Attachment B, for use in the development of a physiologically-based pharmacokinetic (PBPK) model intended to accurately predict the disposition of manganese in target tissues of interest following exposure to different manganese compounds. The Agency believes that the PBPK model and associated experimental database should be robust enough to include variations in Mn exposure concentrations and durations, age, gender and species. The requirements in Attachment B will provide necessary data and information in the development of a Mn PBPK model.

Emission Studies

The Agency has adopted emission speciation testing requirements (described in Attachment C) concerning the Mn particulate which results from the use of MMT in unleaded gasoline at a concentration of up to 1/32 gpg Mn. The objective of these requirements is to better characterize the Mn emission rate and particle speciation of Mn tailpipe emissions from vehicles that utilize MMT in unleaded gasoline. Ultimately, such information would be utilized to help determine the Mn particle atmosphere for each future toxicological study.

Study Protocols and Related Reviews

Development of detailed protocols for each required study is the responsibility of Ethyl (see Attachment A). The protocols must be scientifically valid, responsive to the objectives of the Alternative Tier 2 requirements (as stated in the attachments), and consistent with any specific guidelines specified for the study. Unless otherwise approved by EPA, the protocols for studies required in Attachment B must also conform to the F/FA program guidelines on Good Laboratory Practices.[17]

The protocol for each of the testing requirements which EPA has adopted by today's notification must be subjected to peer review by competent and impartial experts.[18] Each draft protocol subjected to peer review must be revised as appropriate after review of the recommendations of the peer reviewers. The verbatim text of all individual reviewer comments (which may be unattributed), along with a statement of the disposition of each such comment, must accompany the (revised) draft protocol submitted to EPA. Draft study protocols for each required study must be expressly approved by EPA prior to commencement of the studies. EPA will respond in writing,

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[17] 40 C.F.R. § 79.60.

[18] While Ethyl will be responsible for selecting an appropriate and balanced slate of reviewers, EPA is willing to engage in prior consultation with Ethyl on potential candidates.

either approving the protocol, or describing necessary modifications. EPA will make the final determination of whether protocols are acceptable for purposes of the Alternative Tier 2 testing program. The schedule for completion of the Alternative Tier 2 requirements (Attachment D) includes adequate time for protocol development, peer review, and EPA approval. Later protocol changes, if any, must also be approved in advance by EPA.

Additional information on the pharmacokinetics of subacute exposure to inhaled manganese, manganese bioavailability, and nasal uptake of manganese will be necessary to properly design the pharmacokinetic tests EPA is requiring. EPA recognizes that Ethyl and its contractors have already commenced studies intended to provide this required information. However, these studies are not themselves the subject of this notice, and EPA has not formally reviewed and approved the protocols for these studies. Based on the general information concerning these studies provided to EPA as of the date of this action, it appears probable that these studies will provide information necessary to properly design the subsequent pharmacokinetic testing that EPA is requiring. The results of these studies will be evaluated as part of the EPA review and approval process for the testing requirements expressly adopted by EPA.

EPA encourages Ethyl to organize a Technical Advisory Panel (TAP) composed of a cross section of objective scientific experts to help resolve technical issues which arise before and during the implementation of the Alternative Tier 2 regimen.

Future Testing Requirements

EPA may propose additional testing for fuels and additives containing MMT in a second stage of Alternative Tier 2 testing, and may also propose additional testing under Tier 3. The general nature of this additional testing has been previously described by the Office of Research and Development, and has also been discussed extensively with Ethyl. Such additional testing includes neurotoxicity testing on animals, including an investigation of neurobehavioral endpoints in non-human primates. EPA is not formally proposing any additional testing at this time, and will provide separate notification to Ethyl of any further testing to be required.

In addition, the Agency recently received an Ethyl-sponsored report entitled "Manganese Exposure Study (Toronto)"[19] which evaluates personal exposures to manganese and aerosol particulate in the city of Toronto, Canada. The Agency has begun evaluating this report and, at this time, it is not possible to determine what additional exposure studies will be included, if any, in a second stage Alternative Tier 2 notification or under Tier 3. EPA is aware that the results of the recently submitted

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[19] Manganese Exposure Study (Toronto), Research Triangle Institute (RTI/6312/02-01 DF), June 30, 1998.

exposure study may have general implications for risk assessment of MMT and affect the scope of future testing requirements, and EPA will consider this question as part of its review of the study.

Public Comments

EPA received comments on the proposed notification from three parties, the Environmental Defense Fund (EDF), Ford Motor Company (Ford) and the State of Utah. Ethyl submitted some initial comments generally supporting the proposed testing requirements, and also submitted additional comments replying to the comments submitted by other parties.

EDF submitted comments on several aspects[20] of the proposed health testing requirements for MMT on March 30, 1999. EDF commented that they strongly support the inclusion of biomarkers for neurotoxicity in the test protocols. For reasons stated in the EPA's proposed testing requirements and restated above, the Agency has decided on a two-stage approach to health studies, the first stage of which is finalized with this notification and focuses on the development of a pharmacokinetic (PBPK) model capable of predicting manganese disposition, and the second stage of which may be proposed in the future and is expected to focus on toxicity studies. It is EPA's understanding that Ethyl has agreed with EDF to add some additional elements to the pharmacokinetic test program which would accommodate the use of biomarkers and include sufficient testing at known toxic levels to confirm the utility of such biomarkers. EPA does not object to the inclusion of the additional testing agreed to by Ethyl and EDF, so long as it does not interfere with any of the testing requirements adopted today or delay any additional Alternative Tier 2 testing requirements which may be adopted in the future.

EDF commented that the tests as written seem to suggest that non-human primate testing will be required regardless of the results of the first stage of Alternative Tier 2 testing. EDF is not convinced that there is a need to test species other than rodents, as long as all parties are agreed that neurotoxic manifestations do not need to mimic human manganism. EDF wishes to note as a general matter that they believe the use of primates as test subjects in this instance is unnecessary and unjustified. EDF is also concerned about a lack of clarity concerning the use of nonhuman primates as test animals.

As is stated above in EPA's description of the two-stage approach adopted herein, the necessity for and specific elements of the second stage of Alternative Tier 2 testing will be determined later. However, EPA scientists currently anticipate that this

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[20] EPA Air Docket A-98-35, No. IV-D-03, Letter to Air Docket from Ellen Silbergeld and Karen Florini dated March 30, 1999.

second stage may include longer term neurotoxicity and other toxicology testing in the general categories that EPA and Ethyl have been discussing for some time. Such additional testing may include neurotoxicity testing on animals, including non-human primates.

The Agency has extensively reviewed the experimental literature regarding the use of rodent species as test subjects in experimental studies of manganese neurotoxicity.[21] To date EPA has identified over 60 experimental studies published in the scientific literature in which rats and mice were administered a Mn-containing compound by a systemic route of exposure and a neurotoxicological outcome measure was taken. None of these studies have identified an extrapyramidal motor system deficit resembling that known to occur in humans exposed to Mn. Short of behavioral manifestations of motor system deficits, there is a common belief that dopamine depletion in the rodent brain or in the striatum is a neurochemical manifestation of Mn toxicity that could substitute for frank motor deficits. However, the literature is mixed on this issue, with some studies reporting that Mn treatment produces dopamine decreases, other studies reporting dopamine increases, and still other studies reporting no change. The Agency will consider all evidence relating to neurotoxicity and Mn exposure. However, the Agency continues to believe that the non-human primate, not the rodent, is likely to be the most appropriate animal model for obtaining certain types of information on Mn neurotoxicity which EPA may require in the second stage of Alternative Tier 2 testing.

EDF commented that is was not clear how tests in rodents are to be utilized efficiently, if one assumes an eventual requirement of tests in non-human primates. EPA believes that the PBPK model developed in the first stage of Alternative Tier 2 testing will be useful for designing future studies that may be conducted in the second stage. These studies could include not only non-human primate studies to address neurotoxicity but also rodent studies to address respiratory, developmental and reproductive toxicity. In these cases, the PBPK model would help in designing the experimental parameters of the second stage studies, for example, the exposure regime (concentration/dose, route, duration) and age (developmental stage) of the test animals.

Another comment from EDF indicated that actual deposition and accumulation of Mn should be studied rather than relative deposition and accumulation. The Agency does require that actual concentrations of Mn in tissues be measured. As is stated in the requirements (see item 5 in B. Study Requirements, Attachment B), "the study design should include verification of the model predictions with a quantitative

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[21] Boyes, W.K. and Miller, D.B., A review of rodent models of manganese neurotoxicity. Presented at: Manganese: are there effects from long term, low level exposure. Fifteenth International Neurotoxicology Conference, Little Rock, October 26-29, 1997. Neurotoxicology, 19(3), 468, 1998.

determination of Mn in target tissues and other samples resulting from exposure to three manganese compounds". EDF also recommends that uptake and retention should be considered "under conditions of normal Mn intake from the diet and under conditions of reduced Mn intake." As is described in attachment 1 to Appendix B, the on-going manganese research program at CIIT incorporates a standard diet and a Mn-reduced diet.

EDF commented that additional tissue analyses should be included, such as the globus pallidus, substantia nigra and cortex in the list of brain regions, and also the pituitary and adrenal glands. EDF also commented that rather than using the skull cap as the sole bone sample of choice, there should be two samples, the cortical bone (femur) and trabecular bone (vertebrae). EDF also commented that EPA should clarify what is meant by "proper storage" (e.g., for biochemical, histological, or analytical purposes). The Agency has elected to defer the final selection of brain regions and other tissues (including bone) to the protocol development and review/approval process described herein. As a rule, testing requirements establish general parameters and study objectives and do not define all specific study requirements, such as proper storage of tissue samples, specific exposure levels, number of animals per exposure level, etc. The study protocols must be approved by EPA prior to initiation of the studies, and these protocols should provide a detailed description, and an opportunity for peer review, of the selection of tissues to be sampled.

EDF commented that the purpose of seeking post-exposure assessment of Mn pharmacokinetics is unclear. EDF asked if EPA seeks information on half life, depuration, or some other function, and what is the utility of that information? While pointing out that allowing MMT into gasoline will result in continuing exposures to Mn, EDF questions the value of knowing how fast Mn would be removed after cessation of exposure in an experiment. The Agency believes that the purpose of the testing requirements is to develop a PBPK model to predict disposition of Mn following inhalation exposure to Mn compounds. Post-exposure assessment of Mn pharmacokinetics, i.e., Mn clearance from tissues of interest, is critical to the development of the model.

EDF commented that the basis for the selection of the endpoints is unclear in the ongoing study, "Pharmacokinetics of Inhaled Manganese Sulfate in Male CD Rats Following Subacute (14-day) Exposure". EDF stated that as far as it can tell, it has not been demonstrated that these endpoints are sensitive to specific doses of Mn (much less the specific dose and dose/response curve). EDF further commented that, before accepting these endpoints, it is essential to know whether they correlate with neurobehavorial/neuromotor toxicity of Mn in the rodent model, and to have a clear rationale for any and all endpoints. In addition, EDF comments that examination of dopamine transporters, oxidation state, dopamine degrading enzymes such as MAO and COMT should all be included, as should a simple assessment of neurotoxicity in the exposed animals (i.e, EPA's own functional observation battery), along with

assessment of neurodevelopmental landmarks. First, the Agency notes that these are endpoints for the on-going studies being conducted at CIIT and are not endpoints that are formally a part of the testing requirements. The introduction to Appendix 1 of Attachment B of this notice states that "The descriptions of the required pharmacokinetic studies set forth in Attachment B are predicated on an assumption that additional information on the pharmacokinetics of subacute exposure to inhaled manganese, manganese bioavailability, and nasal uptake of manganese will be available to assist Ethyl in the design of these studies. EPA has not elected to formally require studies to develop this necessary information, in recognition of the fact that Ethyl and its contractor the Chemical Institute of Toxicology (CIIT) have already commenced such research." In addition, as explained earlier, EPA does not object to including health outcome testing in this stage of the testing requirements.

Lastly, EDF commented that in the nasal uptake study, it may be necessary to utilize radiotracers to study this with any sensitivity. EPA agrees with this comment, and it is our understanding that Ethyl agrees as well. Ethyl has stated that CIIT intends to use radiotracers in the nasal uptake study. Once again, the study to which this comment pertains is ongoing and is not formally a part of the test requirements in this notification.

Ford commented that "[manganese] silicates should be part of this health study,"[22] because "manganese silicate cannot be excluded as a potential component of the particulate sample." The Agency does not rule out the possibility of Mn-silicon compounds being present in trace quantities but, based on all data reviewed, there is no reason to believe that they may be present in significant quantities. Nevertheless, Ethyl has expressed the willingness to respond to Ford by developing an analytical standard for manganese silicate in order to determine whether the silicate is present in the emission particles which will be analyzed as a result of the speciation requirements in this notification. The Agency believes that incorporation of such a standard for evaluating the particulate samples from the results of the emission speciation test program should address Ford's technical concern. However, since data collected up to this point in time does not indicate a significant probability that manganese silicate is present in significant quantities, no changes to the PBPK requirements will be made to include the testing of silicates.

In this same area, Ford commented that the ongoing Ethyl/CIIT research program does not include hureaulite or manganese sulfate as specified in the testing requirements. In fact, the ongoing program at CIIT does include these compounds. Further peer-reviewed testing protocols resulting from the requirements herein may also include these compounds.

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[22] EPA Air Docket A-98-35, No. IV-D-02, Letter to Air Docket from Walter Kruecher dated March 30, 1999.

Ford also commented that the emission speciation testing should utilize fuel containing MMT during mileage accumulation from the zero mileage point, rather than utilizing MMT only after a 5,000 mile break-in period as proposed. Ford asserted that emissions results would be affected by the use of clear fuel during the "green engine" period. Ford comments that the different break-in protocol (with clear fuel) has been "one of the significant reasons why Ethyl's test results have been different from the auto industry's results." Although the Ford comment may be relevant to certain types of emission testing previously performed by both Ethyl and the auto industry, EPA is unaware of testing performed by the industry to determine the precise nature of the manganese particulate as described in this notification's requirements. It is important to note that the purpose of the emissions program required by this notification is to gather more accurate manganese particulate speciation data. EPA believes it is important to accumulate the initial 5,000 miles on clear fuel to establish a baseline which will enable a comparison of metals content in the engine oil with and without the use of MMT. Therefore, the Agency believes that no change in the requirements is warranted.

Ford also commented that the test fleet in the emission speciation test program should include a light duty truck pair. Ford's reasoning for the inclusion of a light duty truck pair is that a significant portion of the U.S. fleet is made up of light duty trucks or sports utility vehicles, and that since truck emissions may be different than those from cars, the inclusion of a truck pair in the envisioned fleet mix would enhance the emission characterization. The Agency agrees and has revised the emission testing requirements adopted today to include a truck pair or sports utility vehicle pair in the test fleet.

Ford commented that "all maintenance should be performed as prescribed by the vehicle manufacturer" when conducting the emission speciation test program for MMT. Ethyl responded to this comment that they agree and intend to adhere to applicable maintenance recommendations for all of the test vehicles. The Agency also agrees with Ford's comment, that the requirements should provide that all maintenance for the test vehicles be performed as prescribed by the manufacturer's prescribed maintenance schedule and that EPA should retain oversight authority regarding any maintenance that departs from the manufacturer's schedule. Footnote 27 in Attachment C has been modified to include this approach in the test requirements.

Steven C. Packham, Toxicologist for the Department of Environmental Quality, for the state of Utah[23] (state of Utah) commented that the testing program should adopt a study design that specifically addresses threats to sensitive human subjects and that the issues of short-term, transitory exposures (even transitory low-level exposures),

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[23] EPA Air Docket A-98-35, No. IV-D-01, Letter to Air Docket from Steven C. Packhan, Toxicologist for the Department of Environmental Quality, for the state of Utah, dated March 23, 1999

above background levels must be addressed appropriately. The Agency believes that the testing requirements are designed to address concerns for sensitive subpopulations and short-term intermittent exposures. The testing requirements state that tissue samples should be collected from male and female rats as well as tissues collected from rats exposed at different life stages. These requirements address both gender and sensitive subpopulations (see item 3 in B. Study Requirements, Attachment B). Additionally the Agency believes that the testing requirements should result in the development of a physiologically-based pharmacokinetic model to predict tissue Mn dosimetry resulting in different exposure scenarios, including short-term transient excursions above nominal exposure levels. Data for the PBPK model will be derived from both the on-going manganese research program at CIIT that includes 14-day exposure studies and the testing requirements that include 90-day exposure studies as well as the exposure durations in the inhalation study of pregnant female, lactating female and neonatal rats. The Agency concludes that the proposed testing requirements sufficiently address concerns for age-based sensitive subpopulations and short-term intermittent exposures.

The state of Utah also commented that the basic mechanism by which manganese causes Parkinsonian symptoms in sensitive individuals is already known. EPA believes that while it is known that occupational exposure to manganese dioxide induces degenerative changes in the basal ganglia, the cellular and molecular mechanisms by which these changes occur are not known with certainty. The mechanism(s) of action for factors that may render different individuals more sensitive (e.g., nutritional status) are hypothetical. Thus, based on EPA's review of Mn neurotoxicity literature, EPA believes that the basic mechanism by which manganese causes symptoms in sensitive (or normal) individuals is unknown.

Ethyl commented that it supports the Agency's decision to defer imposition of the more comprehensive test program for MMT identified by ORD in 1994 pending (1) development of the pharmacokinetic model for manganese that will be made possible by completion of the testing outlined in this notification letter, and (2) reevaluation of the Agency's 1994 risk assessment for MMT in light of the data developed by Ethyl and submitted to EPA as part of the study entitled, "Manganese Exposure Study (Toronto), Research Triangle Institute (RTI/6312/02-01 DF), June 30, 1998." EPA has separately committed to Ethyl that it will reassess its exposure assessment for use of MMT in unleaded gasoline, and the related risk assessment, in light of the results of the Toronto study. (See the additional letter from Margo T. Oge to Donald R. Lynam which is appended to this letter as Attachment E).

Administrative Procedures

In accordance with the F/FA test program regulations, this letter adopts specific testing requirements comprising the first stage of EPA's Alternative Tier 2 testing regimen and establishes the schedule for completion and submission of such tests.[24] Draft peer-reviewed testing protocols and results, including individual peer review comments, as well as requests for extensions or protocol alterations should be sent to Director, Transportation and Regional Programs Division, Office of Transportation and Air Quality, U.S. EPA (6406J), 1200 Pennsylvania Ave, N.W., Washington, DC 20460.

The EPA contact person who will be available to discuss problems which might arise in implementation of the requirements is Mr. Joe Sopata, Office of Transportation and Air Quality, Transportation and Regional Programs Division, U.S. EPA (6406J), 1200 Pennsylvania Ave, N.W., Washington, DC 20460, phone number (202)564-9034. As needed, Mr. Sopata may also refer such issues to other EPA technical, scientific, or administrative persons for satisfactory resolution.

[24] 40 C.F.R. § 79.58(c)(1).

As required, a copy of this letter adopting specific testing requirements under the Alternative Tier 2 procedures will be placed in Docket No. A-98-35.[25] A Federal Register notice will be issued announcing that EPA has adopted special testing requirements in lieu of or in addition to the standard Tier 2 testing for the MMT atypical gasoline group, and reporting the availability of this notification letter in the public docket.[26]

Sincerely,

Margo T. Oge
Director, Office of Transportation and Air Quality

Attachments:

Attachment A: General Requirements for the First Stage of Alternative Tier 2 Testing of the Atypical Gasoline Additive Methylcyclopentadienyl Manganese Tricarbonyl (MMT)

Attachment B. First Stage Alternative Tier 2 Pharmacokinetic Test Requirements for the Atypical Gasoline Additive MMT

Attachment C. First Stage Alternative Tier 2 Emission Characterization Requirements for the Atypical Gasoline Additive MMT

Attachment D. First Stage Schedule for the Alternative Tier 2 Requirements for the Atypical Gasoline Additive MMT

Attachment E. Letter from Margo T. Oge to Donald R. Lynam, dated **[insert date]**

cc (w/att): J. Michael Davis
Stan Durkee
William Farland
Dorothy Patton
John Hannon
Tim Backstrom

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[25] *Id.*

[26] 40 C.F.R. § 79.58(c)(2).

Attachment A

Fuels and Fuel Additives (F/FA) Health Effects Testing Program: General Requirements for the First Stage of Alternative Tier 2 Testing of the Atypical Gasoline Additive Methylcyclopentadienyl Manganese Tricarbonyl (MMT)

Overview

Attachment A discusses the substances to be tested, testing procedures, the procedure for development of the protocols, and the reporting requirements.

I. Test Substances

1. In accordance with 40 C.F.R. § 79.56(e)(2)(iii), the fuel additive MMT as manufactured by the Ethyl Corporation (Ethyl) falls into the gasoline category of atypical.

2. The pharmacokinetic requirements specify the chemical species of manganese to be evaluated in the pharmacokinetic studies.

II. Conduct of Studies

A. The provisions at 40 C.F.R. § 79.60, when applicable, shall be in effect for purposes of conducting good laboratory practice.

III. Study Protocols

A. For each study required pursuant to this notification, a detailed written peer-reviewed protocol shall be submitted to EPA for review and approved by EPA prior to the initiation of the study. Each protocol will be consistent with the objectives and guidelines specified for the specific test in question and shall include a detailed description of the study design, technical procedures, statistical methods, quality assurance/quality control (QA/QC) procedures, and documentation. Protocols must also provide detailed technical descriptions of the planned experimental design, apparatus, procedures, analytical methods, and documentation.

B. In accordance with Section 79.60(g)(1)(i), the protocols associated with Attachment B must also meet the following criteria:

1. Protocols shall be consistent with applicable provisions of the Good Laboratory Practice (GLP) (Section 79.60), including (but not limited to) provisions regarding safety measures; organization and personnel; facilities; equipment; testing facilities operation; reference substances; protocol for and conduct of a study; records and reports.

2. In the instance that a specified test guideline is found to be inconsistent with the provisions of the GLP, then the provisions of the GLP prevail unless otherwise specified and approved by EPA.

3. To facilitate comparisons of results for different species, study protocols (and performance) shall be standardized to the extent possible.

C. Each protocol shall be submitted in draft form to a group of independent and impartial peer reviewers who possess the appropriate expertise and relevant cross-section of practical experience to provide useful technical critique of the stated methods for meeting testing objectives. While EPA is willing to suggest candidate reviewers, the Ethyl Corporation has responsibility for achieving a scientifically rigorous and objective peer review. At the time the peer review process commences, a copy of each document sent for peer review shall be submitted simultaneously to EPA.

D. Each draft protocol shall be revised as appropriate after review of the recommendations of the individual peer reviewers, and then submitted to EPA for final review and approval. The verbatim comments of each individual reviewer (which may be unattributed), along with a list of all participating peer reviewers and a statement of the disposition of the comments, shall accompany this submission. EPA will respond in writing, either approving the draft protocol as submitted, or describing any required changes along with a timetable for protocol modification.

E. After protocol approval, the studies shall be conducted in accordance with the approved protocols unless a variance is requested in writing and approved in advance by EPA. In unusual circumstances, if an immediate protocol variance is needed to maintain or safeguard the overall integrity of the study, then such action may be taken without prior EPA approval. EPA must be notified of the change in the protocol immediately after the event, including a description of the critical need that required taking the unapproved action and its expected impact on the overall study design and results.

IV. Reporting Requirements

A. Report formatting requirements as specified at 40 C.F.R. § 79.59(c) and (e) shall be used as a guideline for report writing, where applicable.

B. Brief status reports shall be submitted to EPA at six-month intervals while the work continues. The purpose of the status reports is to keep EPA informed of important events, developments, problems encountered or expected, and/or milestones achieved regarding the progress of the work, and should be no longer than necessary to serve this practical purpose. At EPA's option, EPA staff may visit and inspect the laboratory(ies) or other facility(ies) where the Alternative Tier 2 work is being done.

C. At the conclusion of each study, a comprehensive report shall be prepared, including descriptions of the hypothesis tested, QA/QC procedures, the statistical analyses conducted to meet the study objectives, and interpretations of the findings. Such reports shall conform with the general specifications of 40 C.F.R. §79.60(h), where applicable, as well as the reporting requirements included within the particular study protocol.

1. The draft final report shall be submitted in writing to a group of independent and impartial peer reviewers who possess the appropriate expertise and relevant cross-section of practical experience to provide a useful technical critique of the performance of the study and the interpretation of its results. While EPA is willing to suggest candidate reviewers, the Ethyl Corporation has responsibility for achieving a scientifically rigorous and objective peer review. At the time such review commences, a copy of each document sent for review shall be submitted simultaneously to EPA.

2. The draft report shall be revised as appropriate after review of the recommendations of the individual peer reviewers, and then submitted to EPA for review. The verbatim comments of each individual reviewer (which may be unattributed), along with a list of all participating peer reviewers and a statement of the disposition of the comments, shall accompany this submission.

D. The original experimental data shall be retained no less than ten years, and made available to EPA upon request, in printed and electronic format.

V. Modification of Schedules

A. Each required study shall be conducted in accordance with the schedule for that study as set forth in Attachment D. Unless the responsible registrant(s) has requested and EPA has approved a modification of the required schedule pursuant to the procedures set forth below, failure by the responsible registrant(s) to complete a task within the time specified by the schedule shall be considered a failure to satisfy testing requirements and may result in issuance of a notice of intent to cancel affected registrations or any of the other penalties set forth in 40 CFR § 79.51(f). EPA recognizes that unforeseen problems or emergency situations can create unavoidable delays in testing, particularly in tests where novel or unusual testing procedures or technologies are being utilized. Accordingly, the responsible registrant(s) or their designated contractors may at any time request that EPA modify the required schedule for a test. Such a request shall clearly describe the nature of the requested modification of the schedule and provide a detailed explanation of the factual basis for the request. Unless the nature of the emergency requires a more rapid response, EPA will normally respond to each such request within 30 days from receipt of the request by EPA, by either approving the request, denying the request, or requesting additional information. If EPA does not approve or deny such a request within 30 days, the schedule for all subsequent events pertaining to that study shall be automatically extended by the amount of additional time that EPA takes to respond to the request.

B. In any instance where the required schedule for a study provides a specified amount of time for EPA to complete a task, and EPA for any reason takes more than the allotted time to complete that task, the schedule for all subsequent events pertaining to that study shall be automatically extended by the amount of additional time that EPA took to complete that task.

Attachment B
First Stage
Fuels and Fuel Additives Health Effects Testing Program: First Stage
Alternative Tier 2 Pharmacokinetic Test Requirements for the Atypical Gasoline Additive Methylcyclopentadienyl Manganese Tricarbonyl (MMT)

Overview

1. Development of a Physiologically-based Pharmacokinetic (PK) Model to Predict Disposition of Mn in Rats and Nonhuman Primates Following Exposure by Inhalation to Manganese Sulfate, Trimanganese Tetraoxide, and Hureaulite [$MnSO_4$, Mn_3O_4 and $Mn_5(PO_4)_2[PO_3(OH)]_2 - 4H_2O$].

A. Study Objectives:

1. To develop a physiologically-based pharmacokinetic (PBPK) model capable of accurately predicting the disposition of Mn in target tissues and other samples of interest following exposure to three Mn compounds [$MnSO_4$, Mn_3O_4 and $Mn_5(PO_4)_2[PO_3(OH)]_2 - 4H_2O$] for a variety of possible exposure scenarios including variations in exposure concentration and duration. (Model development, dose and duration)

2. To account for possible differences in Mn disposition in potentially susceptible members of the population including those based on age or gender. (Sensitive sub-populations and gender effects)

3. To examine possible differences in disposition of Mn in rodents and non-human primates, and to be able to make predictions for Mn disposition in humans. (Species differences)

4. To determine the relative deposition and accumulation of Mn in target tissues and other samples resulting from inhalation exposure to three Mn compounds [$MnSO_4$, Mn_3O_4 and $Mn_5(PO_4)_2[PO_3(OH)]_2 - 4H_2O$]. (Form of Mn compound)

5. Optional: To determine whether an alternative route of exposure can be used to conduct health outcome studies in lieu of the inhalation route. If Ethyl Corporation chooses to investigate any routes of exposure in addition to inhalation, the study/studies should examine disposition of Mn as a function of exposure route in order to determine if a route of exposure other than inhalation is appropriate for health outcome studies. (Route extrapolation)

B. Study Requirements:

In meeting the objectives, the study design:

1. should result in the development of a PBPK model capable of predicting Mn disposition including concentrations of Mn in target tissues [e.g., brain (brain regions including olfactory bulb, striatum, cerebellum, hippocampus, hypothalamus, and rest of brain), lung, reproductive organs, liver], blood, bile and feces (or colon/gut content). Separate data sets should be used for model development and verification. (Model development)

2. should include verification of model predictions under a variety of conditions including changes in exposure concentration and duration. Appropriate exposure concentration and duration studies would involve four exposure levels including controls for the 90-day inhalation exposure of rats, 90-day inhalation exposure of non-human primates, and developmental study in rats, as well as the exposure concentrations and durations employed in the on-going manganese research program being sponsored by Ethyl Corporation (see Appendix 1 to this attachment). (Dose and duration)

3. should include verification of model predictions with tissue samples collected from male and female rats as well as from tissues collected from rats exposed at different life stages including gestational (e.g., day 18), weaning (e.g., postnatal day 21), juvenile (e.g., postnatal day 35), young adult (e.g., postnatal day 70), and senescent (e.g., $\geq$ 18 months) animals. (Sensitive subpopulations and gender effects)

4. should include verification of model predictions with target tissue samples, collected from exposed rats and exposed non-human primates. (Species differences)

5. should include verification of the model predictions with a quantitative determination of Mn in target tissues and other samples resulting from exposure to three Mn compounds [$MnSO_4$, Mn_3O_4 and $Mn_5(PO_4)_2$ $[PO_3(OH)]_2$ - $4H_2O$]. (Form of Mn compound).

6. should include verification of model predictions with target tissue samples collected from animals exposed via inhalation and with other routes of exposure (if studies of other routes of exposure are conducted in addition to the required inhalation exposure). (Route extrapolation)

C. Study Descriptions

1. Design of 90-day rat inhalation study

   - should include inhalation exposure to primary manganese species (control and three exposure concentrations) and a secondary species (at the same nominal concentration as the highest concentration for the primary manganese species) for 6 hours/day, 5 days/week, for 13 weeks.

   - should include adult (10 week old) male and female rats and aged (> 18 month old) male rats.

   - should include evaluation of tissues at appropriate time intervals, including total Mn concentrations in blood, pancreas, brain (olfactory bulb, striatum, cerebellum), lung, liver, testes or ovaries, and femur. Should also include collection of the following tissues at necropsy: pancreas, blood (serum, erythrocytes), brain (olfactory bulb, striatum, cerebellum, hippocampus, hypothalamus, rest of brain) lung, liver, femur, skull cap, skeletal muscle, heart and reproductive organs.

   - should include post-exposure assessment of Mn pharmacokinetics.

2. Design of inhalation study of pregnant female, lactating female and neonatal rats.

   - should include inhalation exposure to a single manganese species (control and three exposure concentrations) for 6-hr/day, 7 days/week as follows:

     - 14 days prior to mating (F0 male and female rats);
     - up to 14 days during mating period (F0 male and female rats);
     - 18 days following gestation day (GD) 0 (presumed pregnant F0 rats); and
     - up to 19 days commencing on post natal day (PND) two through PND 21 (both dams and their pups).

   - should include adult (10 week old) female (both pregnant and lactating) rats and neonatal rats.

   - should include evaluation of total Mn concentrations in maternal and fetal brain, blood, liver, and bone following GD 18 exposure, as well as collection of the following maternal tissues: pancreas, placenta, lung, skull cap, skeletal muscle, heart and reproductive organs (ovary).

     - Pup recovery groups at 4 and 8 weeks post exposure.

- should include evaluation of total Mn concentrations in neonatal and maternal serum, olfactory bulb, striatum, cerebellum, lung, liver and femur at appropriate time intervals, as well as collection of the following tissues from each dam and pup; pancreas, blood (erythrocytes), hippocampus, hypothalamus, rest of brain, lung, skull cap, skeletal muscle, heart and reproductive organs (testes, ovary). Tissue Mn levels in pups will be determined at weaning and at two post-weaning time points following cessation of inhalation exposure.

- should include proper storage of all tissue samples collected, but not analyzed for Mn content.

3. Design of 90-day primate inhalation study.

   - should include inhalation exposure to a single manganese species (control and three exposure concentrations) for 6 hours/day, 5 days/week for 13 weeks.

   - should include juvenile (11-15 month old) rhesus monkeys.

   - should include evaluation of tissues at appropriate intervals, including total Mn concentrations in blood, brain regions (including putative target sites - e.g., putamen), lung, liver, femur, skull, pancreas, skeletal muscle, testes and heart.

Appendix 1 to Attachment B.

On-going Manganese Research Program at the Chemical Industry Institute of Toxicology (CIIT)

The descriptions of the required pharmacokinetic studies set forth in Attachment B are predicated on an assumption that additional information on the pharmacokinetics of subacute exposure to inhaled manganese, manganese bioavailability, and nasal uptake of manganese will be available to assist Ethyl in the design of these studies. EPA has elected not to formally require studies to develop this necessary information, in recognition of the fact that Ethyl and its contractor the Chemical Industry Institute of Toxicology (CIIT) have already commenced such research. EPA has not reviewed or approved the protocols for any of these ongoing studies. Based on the general information provided to EPA to date, it appears probable that these ongoing studies will provide information which is necessary to properly design the required studies as described in Attachment B. EPA expects that the results of these ongoing studies will be utilized as appropriate by Ethyl in design of the required studies and submitted to EPA along with the draft protocols for the studies to be required by EPA. The ongoing studies being conducted by Ethyl and CIIT are described below.

Study 1: Pharmacokinetics in Inhaled Manganese Phosphate in Male CD Rats Following Subacute (14-Day) exposure. (Completed)

- Nominal Mn phosphate inhalation exposure concentrations of 0.0, 0.03, 0.3, and 3 mg Mn/m^3 for 6 hours per day for 14 days (14 exposures).
- Tissue collection: blood (serum, erythrocytes), brain (olfactory bulb, striatum, cerebellum), lung, liver, femur, skull cap, skeletal muscle and heart.

Study 2: Pharmacokinetics of Inhaled Manganese Sulfate ($MnSO_4$) in Male CD Rats Following Subacute (14-Day) exposure.

- Nominal Mn sulfate inhalation exposure concentrations of 0.0, 0.03, 0.3 and 3 mg Mn/m^3 for 6 hours per day for 14 days (14 exposures), 12 rats per exposure concentration.
- Two different dietary manganese levels – i.e., standard NIH-07 diet (100 ppm Mn) or a Mn-reduced diet (approximately 25 ppm Mn).
- Tissue collection: blood (serum, erythrocytes), brain (olfactory bulb, striatum, cerebellum), lung, liver, femur, skull cap, skeletal muscle and

heart. Total Mn concentrations in serum, bile, olfactory bulb, striatum, cerebellum, lung, liver, and femur will be determined following the last exposure (6 rats/sample) using neutron activation or another suitable analytical technique.

- Endpoints used to evaluate the functional status of the nervous system following Mn exposure:

  - Tyrosine hydroxylase (TH) activity
  - TH protein levels
  - TH mRNA levels
  - D1 dopamine receptor mRNA levels
  - D2 dopamine receptor mRNA levels
  - Metallothionein (MT) protein levels
  - MT mRNA levels
  - Glutamine synthetase (GS) activity
  - GS protein levels
  - GS mRNA levels

Study 3: Pharmacokinetics of Inhaled Manganese Tetraoxide (Mn_3O_4) in Male CD Rats Following Subacute (14-Day) exposure.

- Nominal Mn tetraoxide inhalation exposure concentrations of 0.0, 0.03, 0.3 and 3 mg Mn/m^3 for 6 hours per day for 14 days (14 exposures), 12 rats per exposure concentration.

- Two different dietary manganese levels – i.e., standard NIH-07 diet (100 ppm Mn) or a Mn-reduced diet (approximately 25 ppm Mn).

- Tissue collection: blood (serum, erythrocytes), brain (olfactory bulb, striatum, cerebellum), lung, liver, femur, skull cap, skeletal muscle and heart. Total Mn concentrations in serum, bile, olfactory bulb, striatum, cerebellum, lung, liver, and femur will be determined following the last exposure (6 rats/sample) using neutron activation or another suitable analytical technique.

- Endpoints used to evaluate the functional status of the nervous system following Mn exposure:

  - Tyrosine hydroxylase (TH) activity
  - TH protein levels
  - TH mRNA levels
  - D1 dopamine receptor mRNA levels
  - D2 dopamine receptor mRNA levels

- Metallothionein (MT) protein levels
- MT mRNA levels
- Glutamine synthetase (GS) activity
- GS protein levels
- GS mRNA levels

Study 4: Manganese Bioavailability by Route of Exposure

- Objective: To determine how Mn is partitioned in blood and possible target tissues of CD rats following exposure to Mn via toxicologically relevant routes of exposure.

- Adult CD rats using oral, pulmonary, intravenous, and inhalation (nose only) routes of $MnCl_2$ delivery.

- Tissue and blood analyses.

Study 5: Manganese Nasal Uptake Study

- Objective: To determine whether direct nasal uptake of Mn to the brain can occur following Mn inhalation.

- Development of nasal preclusion technique using a custom-designed plastic nose pellet.

- A comparison of Mn concentrations found in the olfactory bulbs (patent vs. occluded sides) will provide a semi-quantitative estimate of the contribution made by direct nasal uptake of manganese.

Attachment C

First Stage Alternative Tier 2 Emission Characterization Requirements for the Atypical Gasoline Additive MMT

Overview

Attachment C describes the specific requirements of the Alternative Tier 2 emission characterization requirements for the atypical gasoline additive group of MMT. It identifies the objectives of the testing program for this group, and identifies the specific testing requirements.

A. General objectives:

1) To develop additional data regarding manganese (Mn) emission particulate speciation characterization and the manganese emission rate that results from using MMT in the combustion of unleaded gasoline.

2) Together with existing manganese speciation and manganese emission rate data and information from the pharmacokinetic studies in Attachment B, this information should assist in refining the risk assessment for MMT and in making judgments as to the Mn particle atmosphere for further health effects testing of animals, if any.

B. The required testing includes mileage accumulation, particulate collection and appropriate analytical analysis of the manganese particulate and manganese emission rates.

C. The requirements in Attachment A apply to the extent specified therein.

D. Together with information from the pharmacokinetic studies in Attachment B and the information provided by the Ethyl Corporation in their 1997 report "Characterization of Manganese Particulates from Vehicles using MMT Fuel", this new characterization should assist in making judgments as to the Mn particle atmospheres for each future toxicology study of animals, if any.

Specific Requirements

I. Emission Speciation Characterization Requirements for Mn particulate generated on a Chassis Dynamometer.

1) *Fleet Composition.* Particulate emission tests shall be conducted on a fleet of vehicles using EPA-approved emissions test methods and procedures. The test fleet shall:

A. be described in detail;
B. be selected for representativeness of in-use gasoline-fueled vehicles[27];
C. have a minimum of six vehicles that include 3 models, two vehicles per model that include two 4-cylinder vehicles, two 1997 Ford Taurus V-6 powered vehicles (Ethyl Tier One vehicles) and two V-8 powered sports utility vehicles or two V-8 powered light duty truck vehicles;
D. be tested over a range of 50,000 miles with MMT fuel blended at 1/32 g Mn/gal;
E. use MMT fuel possessing similar chemical and physical fuel specifications for all testing[28] (*i.e.*, both mileage accumulation and dynamometer testing).

2) *Vehicle Mileage Accumulation:* All mileage will be accumulated using an accelerated mileage accumulation driving cycle. (See Appendix 1 to Attachment C).

The new vehicles will accumulate 5,000 miles on the driving cycle using a base fuel that does not contain the MMT fuel additive. This baseline will facilitate used oil evaluations (see section 4, Oil Changes and Oil Analysis). After accumulating 5,000 miles as a baseline, the vehicles will accumulate an additional 50,000 miles using a fuel possessing similar chemical and physical

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[27] The protocol must provide for prior EPA approval of any maintenance outside of regularly scheduled maintenance, including replacement or modification of components that come into contact with MMT or its combustion products, unless the maintenance is necessary to maintain the normal operation or safety of the test vehicle (e.g., replacement of worn or broken fan belts, battery replacement, brake adjustments, etc.).

[28] Although this situation is not expected to happen, since the MMT fuel is required to posses similar chemical and physical specifications, any fuel constituent changes that are made during the entire period of mileage accumulation and emission testing shall be reported to EPA in the periodic status reports required by Attachment A, Section IV, paragraph B.

specifications with MMT at a concentration of 1/32 g Mn/gal. Particulate emission tests will be performed after accumulating 5,000, 25,000 miles and 50,000 test miles on MMT fuel, corresponding to odometer readings of 10,000, 30,000 and 55,000 miles.

The two 1997 Taurus will accumulate miles on the mileage accumulation driving cycle using the same MMT fuel. After accumulating 5,000 test miles (in addition to the nominal 50,000 miles already accumulated on these vehicles using MMT fuel), the vehicles will undergo particulate testing. The vehicles will then continue to accumulate mileage using the same cycle and schedule as the new vehicles, with particulate emission tests at 25,000 and 50,000 additional miles, corresponding to nominal odometer readings of 75,000 and 100,000 miles. Thus, particulate testing will occur for these vehicles at nominal odometer readings of 55,000, 75,000 and 100,000 miles.

3) *Test Fuel:* A base fuel that does not contain the fuel additive MMT will be used for the initial 5000 miles of break-in mileage accumulation for the new vehicles. Subsequent mileage accumulation (all mileage accumulation for the Taurus vehicles) and all particulate emission testing will be performed using the fuel containing MMT at a concentration of 1/32 g Mn/gal.

4) *Oil Changes and Oil Analysis.* The same type/lot of commercial oil will be used in each model throughout the testing. Vehicles will undergo an oil change every 5,000 miles. Oil consumption will be recorded at every change. The new oil and oil from changes at 0, 5,000, 25,000, and 50,000 test miles will be subjected to elemental analysis to determine the elemental content of phosphorous, zinc, manganese, calcium, and iron. Oil analyses after the 5,000 mile break-in (0 test miles) on the base fuel will be used to construct a relationship between Mn and Fe introduced into the lubricant due to engine wear. In the used oil samples the Fe level will be used as a tracer to approximate the contribution of engine wear to Mn levels in oil. After accounting for engine wear, remaining Mn is expected to arise due to MMT use. The purpose of the oil analysis is to better define the relationship between oil use and manganese phosphate formation.

5) *Vehicle Preparation:* The same fuel containing MMT will be used for mileage accumulation, vehicle preparation and particulate emission testing. After inspection of the vehicle to ensure it is dynamometer-ready and after conducting routine maintenance, the fuel tank will be filled with MMT fuel. Particulate emission testing will follow the procedure outlined in section 6 of this attachment.

6) *Particulate Sample Generation:* Particulate will be collected from the vehicles on a dynamometer using the procedures refined during the previous speciation program. These techniques are based on EPA particulate sampling procedures as described in CFR 40 part 86. Particulate collection is divided into two periods

per day for each particulate sampling cycle employed in the testing and will take place over two days at each particulate collection point. The composite cycle composed of the REMO and REPO (REMO/REPO) cycles (see Appendix 2 of Attachment C) will be used for particulate generation. Although not part of these requirements, the Ethyl Corporation has expressed a desire to generate additional particulate samples on the Urban Dynamometer Driving Schedule (UDDS), more commonly referred to as the LA4. Three samples based on particulate size will be collected, $PM_{2.5}$, PM_{10} and TSP. Particulate samples will be collected over all repetitions of the driving cycle during the sample period.

The vehicles will undergo 2 days of sampling (one day for each particulate sampling cycle employed in the testing), with the 4 cylinder and 8 cylinder vehicles sampled at 10,000, 30,000 and 55,000 odometer miles, and the 6 cylinder vehicles at nominal 55,000, 75,000, and 100,000 odometer miles, to accommodate Ethyl Corporation's desire to employ the LA4 cycle in the test program, in addition to the required REMO/REPO cycle. At 10,000 miles, the test schedule is as follows: the first day, after an LA4 prep the night before, particulate will be collected over 2 sample periods. During the first (morning) sample period and second (afternoon) period, particulate will be collected during both periods over 7 repeats of the LA4. On the second day, particulate collection is again split into morning and afternoon periods, where particulate will be collected during both periods over the required composite REMO/REPO cycle described in Appendix 2 to this attachment. This schedule is provided in detail in Appendix 3 to Attachment C.

The $PM_{2.5}$, PM_{10} and TSP samples will be collected over all repetitions of the cycle.

Gaseous emission tests for hydrocarbons, oxides of nitrogen, and carbon monoxide will be performed during each required sample generation period in order to verify the integrity and repeatability of the particulate sample collection. The gaseous emission results may be reported as a value of one for the first testing period. For the second testing period, the gaseous emission results may be reported as a multiple or fraction of the gaseous emission results from the first period. Specifically, the second period's gaseous emissions for each emittant, for each sample generation cycle, may be reported as:

$$\frac{\text{1st sampling period's emission results}}{\text{2nd sampling period's emission results}}$$

Because the sole purpose of gaseous emission testing is to verify the integrity and repeatability of the sample generation procedures, absolute values for gaseous emissions need not be reported.[29]

7) *Analytical Methods.* Standard operating procedures (or equivalent) for analytical methods for quantitative particle speciation shall be provided to EPA prior to testing.

   A. A portion of the $PM_{2.5}$ and TSP particulate samples will undergo Mn speciation analysis, while the PM_{10} particulate samples and remaining replicate particulate samples will be retained to preserve the option of manganese speciation analysis at a later date (as specified in Appendix 4 to Attachment C).

   B. Standard techniques for elemental analysis will be employed to evaluate and report the total manganese, sulfur, and phosphorous in the $PM_{2.5}$, and TSP fractions. Any elements to be analyzed other than Mn, S and P will be determined in the protocol development process once the appropriate analytical method(s) to analyze the manganese particulate have been specified. Elemental analysis will also be used to determine the Mn, P, Ca, Zn and Fe content of the new and used oil samples.

   C. The amounts of manganese oxides (MnO, Mn_2O_3, and Mn_3O_4), manganese phosphates and manganese sulfates ($MnSO_4$) shall be reported in mg/mile (micrograms/mile) and as a percentage of the total Mn emitted in both the $PM_{2.5}$ and TSP fractions.

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[29] This speciation test program is not designed or intended to address the effect of MMT use on emissions of any regulated gaseous pollutants. This issue was directly addressed by test data previously submitted by Ethyl, which led to a determination by EPA that use of MMT at 1/32 gram manganese per gallon gasoline does not cause or contribute to emission control system failures. See 59 FR 42227 (August 17, 1994). For purposes of this speciation program, the measurement of gaseous emissions is designed exclusively to verify the integrity and repeatability of the particulate sample collection. Because these speciation tests will not include any control vehicles utilizing fuels without MMT and because of general uncertainty surrounding the effects of the mileage accumulation driving cycle on emission control system durability, EPA has determined that this study cannot be construed as identifying or measuring the gaseous emission products of MMT, the effect of MMT on gaseous emissions, or the effects of the emission products of MMT on the performance of emission control devices or systems.

D. The proposed program will generate 108 samples for elemental analysis, 48 samples for manganese speciation and 30 oil samples for analysis (See Appendix 4 to Attachment C). As is described in Appendix 4 to this attachment, should significant discrepancies be observed between speciation results for the first and second particulate collection periods using the requisite REMO/REPO cycle at the 30,000 mile interval (75,000 for the 6-cylinder vehicles), speciation of particulates obtained from the second particulate collection period will also be performed on the set of samples obtained from the second particulate collection period at the 55,000 mile interval (100,000 for the 6-cylinder vehicles).

8) *Reporting of Results of Mn Speciation Analysis.*

A. Reports of the results of analyses for PM2.5 and TSP shall include results in the following 11 Mn categories:

1) Total Mn $PM_{2.5}$ (or TSP) emitted in micrograms/mile.
2) MnO emitted in micrograms/mile.
3) MnO as percent of total Mn.
4) Mn_2O_3 emitted in micrograms/mile.
5) Mn_2O_3 as percent of total Mn.
6) Mn_3O_4 emitted in micrograms/mile.
7) Mn_3O_4 as percent of total Mn.
8) Mn(PHOS) emitted in micrograms/mile.
9) Mn(PHOS) as percent of total Mn.
10) $MnSO_4$ emitted in micrograms/mile.
11) $MnSO_4$ as percent of total Mn.

9) *Reporting of Results of Elemental Particulate Analysis.*

A. For each particulate fraction undergoing elemental analysis, the following should be reported.

1) Total $PM_{2.5}$ (or TSP) in micrograms/mile.
2) Mn emitted in the particulate in micrograms/mile.
3) P emitted in the particulate in micrograms/mile.
4) S emitted in the particulate in micrograms/mile.
5) Mn percent of particulate fraction.
6) Percent of fuel Mn emitted from tailpipe.
7) P percent of total particulate fraction.
8) S percent of total particulate fraction.
9) Information for other elements analyzed shall be reported.

Appendix 1 to Attachment C: Mileage Accumulation Driving Cycle

Event	Cruise Speed (mph)	No. Of Stops	Time per Stop (sec.)	Accel. Rate	Comments
1	60	2	0	Mod	
2	60	2	0	Mod	
3	60	2	15	WOT	Key off at stops
4	60	2	15	WOT	Engine idle at stops
5	70	0	NA	Mod	
6	80	0	NA	Mod	
7	70	0	NA	NA	
8	70	0	NA	NA	
9	70	0	NA	NA	
10	70	0	NA	NA	
11	70	1	30	NA	Engine idle at stop
12	55	1	300	Mod	Key off at stop (5 min)
13	35	1	30	Light	Engine idle at stop
14	45	1	30	Mod	Engine idle at stop
15	30	4	15	Light	Includes 5 decels to 10 mph
16	30	4	15	Light	Includes 5 decels to 10 mph
17	40	4	15	Light	Includes 5 decels to 10 mph
18	55	1	300	Mod	Engine idle at stop

Notes:

Each event is 4 miles, each cycle of 18 events is 72 miles.

No. of stops includes the no. of mid-event stops plus the stop at the end of the event (the stop at the beginning of the event is tabulated as the end stop of the previous event).

Once a day the vehicle is cold soaked for 8 hours, then cold started.

Appendix 2 to Attachment C: Dynamometer Cycles

Particulate will be generated using the composite REMO/REPO driving cycle. Although not part of these requirements, the Ethyl Corporation has expressed a desire to generate additional particulate on the Urban Dynamometer Driving Schedule (UDDS), commonly referred to as the LA4 driving cycle.

During an LA4 sample period, 7 repeats of the LA4 will be performed.

The REMO portion of the REMO/REPO composite cycle is composed of two fractions: a "start" fraction lasting four minutes followed by a "remnant" fraction lasting twenty-one minutes. The "start" fraction represents driving patterns which occur during the first four minutes after starting a vehicle. The "remnant" fraction represents that portion of in-use driving which is not represented by either the start cycle or the higher speed REPO cycle. The REPO portion of the composite cycle is also comprised of two fractions: a high speed freeway portion with speeds to 80 mph lasting 20 minutes followed by a high acceleration portion lasting three and one-half minutes.

The REMO/REPO composite cycle for purposes of this action shall consist of 8 REMO and 2 REPO cycles. During a REMO/REPO sample period, the combination of 2 REMO and 1 REPO cycle is repeated twice and particulate collection terminates with a final repeat of 4 REMO cycles. While this combination closely reflects the relative fractions of time on the dynamometer that are equivalent to conventional and higher speed/higher acceleration driving fractions under actual in-use conditions, EPA will accept as an alternative a final repeat of 2 REMO cycles in lieu of 4 REMO cycles at the end. This would result in less dynamometer testing time, without sacrificing the integrity of the test program given EPA's goal of attempting a general Mn particle characterization of the fleet that encompasses all conditions. This cycle is illustrated below in Table 1. Between each REMO and REPO there is a 10 minute soak.

Table 1. REMO/REPO Composite Cycle

	Time (sec)
REMO	1494
10 minute soak	600
REMO	1494
10 minute soak	600
REPO5	1400
10 minute soak	600
REMO	1494
10 minute soak	600

REMO	1494
10 minute soak	600
REPO5	1400
10 minute soak	600
REMO	1494
10 minute soak	600
REMO	1494
Total	15964 (4 hours 26 minutes)

Appendix 3 to Attachment C: Dynamometer Testing Schedule

Particulate sample generation will occur over two days to accommodate Ethyl Corporation's desire to obtain additional particulate samples on the LA4 driving cycle. Each day is broken into two sample periods to give a total of 4 sample periods at each mileage point. At each mileage point, the REMO/REPO composite cycle will be used to produce particulate over two periods. Vehicles will be sampled at 10,000, 30,000 and 55,000 test miles. The scheduling of the sample periods over the two days of testing for both the required REMO/REPO cycle and the LA4 cycle is presented in Table 1. All 6 vehicles use the same driving schedule.

Table 1. Driving Cycle Schedule for Particulate Collection. The illustration is for both vehicle 1 and vehicle 2 in one model type.

Odometer Reading		**10K (55K for 6-cyl.)**		**30K (75K for 6-cyl.)**		**55K (100K for 6-cyl.)**	
Collection Period		**1**	**2**	**1**	**2**	**1**	**2**
Vehicle 1 & Vehicle 2	Day 1	LA4*	LA4*	LA4*	LA4*	LA4*	LA4*
	Day 2	REMO/ REPO	REMO/ REPO	REMO/ REPO	REMO/ REPO	REMO/ REPO	REMO/ REPO

* Although not part of this Dynamometer Testing Schedule, the Ethyl Corporation has expressed a desire to obtain additional particulate samples on the LA4 driving cycle.

Appendix 4 to Attachment C: Sample Generation and Analysis

At each sample point the 6 test vehicles will generate 36 samples used to determine manganese emission rate and 36 samples used to determine manganese speciation and 6 oil samples for elemental analysis. Manganese speciation analysis will be carried out on $PM_{2.5}$ and TSP collected during the first collection period using the required REMO/REPO cycle for all vehicles. At the 30K mileage interval, all $PM_{2.5}$ and TSP filters collected from all vehicles for both the first and second REMO/REPO collection periods will be analyzed. All other samples collected for Mn speciation from the second collection period will be stored and analyzed only to resolve significant discrepancies in the data. Overall, 108 samples will be analyzed to determine the manganese emission rate, 48 samples will undergo manganese speciation and 30 oil samples will be analyzed. Aggregate sample generation is summarized in Table 1. The manganese emission rate analyses, manganese speciation analyses and oil sample analyses are summarized in Table 2.

Analysis of the stored filters would be considered only to resolve significant discrepancies in the data. Should significant discrepancies be observed between speciation results for the first and second collection period samples collected at the 30,000 mile interval (75,000 for the 6-cylinder vehicles), speciation of particulates will also be performed on the samples from the second collection period using the REMO/REPO cycle at the 55,000 mile interval (100,000 for the 6-cylinder vehicles).

Table 1: Aggregate sample generation for each vehicle at end of testing.

Vehicle	1	2	3	4	5	6	Total
Elemental Mn, S, P Emissions [b]							108
TSP	6	6	6	6	6	6	
PM10	6	6	6	6	6	6	
PM2.5	6	6	6	6	6	6	
Manganese Speciation							108
TSP	6	6	6	6	6	6	
PM10(a)	6	6	6	6	6	6	
PM2.5	6	6	6	6	6	6	
Oil Analysis-Mn, P, Ca, Zn, and Fe	5	5	5	5	5	5	30

(a) Samples will be collected but not subjected to analysis unless there is a need to resolve significant discrepancies in the data.
(b) Other elements may be analyzed as described in Attachment C, Section I.7.B.

Table 2. Total samples for analysis.

Odometer Reading	10K (55K for 6-cyl)	30K (75K for 6-cyl)	55K (100K for 6-cyl)	Total
Model	**Manganese Emission rate**			
M1 (2 vehicles)	12	12	12	36
M2 (2 vehicles)	12	12	12	36
M3 (2 vehicles)	12	12	12	36
Total	36	36	36	108
	Manganese Speciation			
M1 (2 vehicles)	4*	8**	4	16
M2 (2 vehicles)	4	8	4	16
M3 (2 vehicles)	4	8	4	16
Total	12	24	12	48
Oil Samples				
M1 (2 vehicles)	2	2	2	6
M2 (2 vehicles)	2	2	2	6
M3 (2 vehicles)	2	2	2	6
Base Oils				12
Total	6	6	6	30

Notes:

M1 – Model 1
M2 – Model 2
M3 – Model 3
* - speciation of samples obtained from the first particulate collection period
**- speciation of samples obtained from both particulate collection periods

Attachment D

First Stage Schedule for the Alternative Tier 2 Requirements for the Atypical Gasoline Additive MMT

1) Schedule for Health Study (PK study).

The development of a physiologically-based PK model capable of accurately predicting the disposition of Mn in target tissues of interest following exposure to three Mn compounds will involve exposures of different durations (e.g., 90-day exposures) and different species (rats and non-human primates). The three schedules below are based on the following assumptions:

- rats (young adults and aged animals) will be exposed by inhalation for 90 days (Schedule D.1),
- rats will be exposed by inhalation in a developmental study (Schedule D.2), and
- non-human primates will be exposed by inhalation for 90 days (Schedule D.3).

SCHEDULE D.1 (90-day exposure of young adult and aged rats)

Ethyl submits draft peer-reviewed protocol including individual peer review comments (which may be unattributed) and disposition of comments	4 months[a]
EPA provides comments on draft protocol to Ethyl	6 months
Ethyl submits revised draft protocol to EPA	8 months
EPA approves/disapproves revised draft protocol	10 months
Ethyl submits draft final report for review by EPA including individual peer review comments (which may be unattributed) and disposition of comments	26 months
EPA provides comments on draft final report	28 months
Ethyl submits final report to EPA	30 months

[a] Schedule commences February 1, 2000, or when all the pharmacokinetic studies in Appendix 1 to Attachment B have been completed, whichever is earlier.

SCHEDULE D.2 (Developmental study of rats)

Ethyl submits draft peer-reviewed protocol including individual peer review comments (which may be unattributed) and disposition of comments	15 months[a]
EPA provides comments on draft protocol to Ethyl	17 months
Ethyl submits revised draft protocol to EPA	19 months
EPA approves/disapproves revised draft protocol	21 months
Ethyl submits draft final report for review by EPA including individual peer review comments (which may be unattributed) and disposition of comments	33 months
EPA provides comments on draft final report	35 months
Ethyl submits final report to EPA	37 months

SCHEDULE D.3 (90-day exposure of primates)

Ethyl submits draft peer-reviewed protocol including individual peer review comments (which may be unattributed) and disposition of comments	26 months[a]
EPA provides comments on draft protocol to Ethyl	28 months
Ethyl submits revised draft protocol to EPA	30 months
EPA approves/disapproves revised draft protocol	32 months
Ethyl submits draft final report for review by EPA including individual peer review comments (which may be unattributed) and disposition of comments	47 months
EPA provides comments on draft final report	49 months
Ethyl submits final report to EPA	51 months

2) Schedule for Mn Tailpipe Emissions Characterization Study

Ethyl submits draft peer-reviewed protocol together with individual peer review comments (which may be unattributed) and disposition of comments	6 months[b]
EPA provides comments on draft protocol to Ethyl	7 months
Ethyl submits revised draft protocol to EPA	8 months
EPA approves/disapproves revised draft protocol	9 months
Ethyl initiates automobile particle testing	11 months
Ethyl finishes Mn particulate sampling and mileage accumulation	26 months
Ethyl completes elemental and speciation analysis	32 months
Ethyl submits draft final report for review by EPA together with peer review comments (which may be unattributed) and disposition of comments	38 months
EPA provides comments on draft final report	40 months
Ethyl submits final report to EPA	42 months

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[b] Schedule commences upon receipt by Ethyl of this letter adopting Alternative Tier 2 study requirements.

Attachment E

Letter from Margo T. Oge to Donald R. Lynam

MAY 11 2000

Donald R. Lynam, Ph.D., CIH, P.E.
Vice President, Air Conservation
Ethyl Corporation
330 South Fourth Street
Richmond, VA 23219-4304

Dear Dr. Lynam:

In a separate letter today, I notified you of the decision by EPA to adopt specific testing requirements for MMT under the Alternative Tier 2 provisions of the fuel and fuel additive health effects testing regulations. I want you to know that I appreciate the constructive manner in which Ethyl and its contractors have worked with EPA personnel to develop these interim testing requirements. EPA expects that the data developed pursuant to these testing requirements will be very helpful in evaluating the specific nature and scope of any further Alternative Tier 2 testing. It is my understanding that Ethyl has accepted and intends to satisfy the current testing requirements.

While testing to satisfy the interim requirements adopted today is underway, EPA agrees that it will reevaluate its prior exposure assessment for use of MMT in unleaded gasoline, and the related risk assessment, in light of the data developed and submitted to EPA as part of the study entitled "Manganese Exposure Study (Toronto), Research Triangle Institute (RTI/6312/02-01 DF), June 30, 1998" [hereafter "the Toronto study"]. After completing this review, EPA will make any revisions of these assessments it deems appropriate in light of this information.

EPA also agrees that it will afford Ethyl an opportunity to comment on its analysis of the Toronto study and on any related revisions of its exposure assessment and risk assessment for use of MMT in unleaded gasoline, before adopting any specific findings pertaining to the Toronto study, making any final revisions in the exposure and risk assessments, or proposing any additional testing requirements for MMT.

I trust that this letter accurately states the nature of our understanding, and hope that all future discussions pertaining to potential testing requirements for MMT will continue in the constructive manner of the discussions to date.

Sincerely,

Margo T. Oge
Director, Office of Transportation and Air Quality