§79.54 Tier 3.

(a) General Criteria for Requiring Tier 3 Testing. (1) Tier 3 testing shall be required of a manufacturer or group of manufacturers at EPA's discretion when remaining uncertainties as to the significance of observed health effects, welfare effects, and/or emissions exposures from a fuel or fuel/additive mixture interfere with EPA's ability to make reasonable estimates of the potential risks posed by emissions from the fuel or additive products. Tier 3 testing may be conducted either on an individual basis or a group basis. If performed on a group basis, EPA may require either the same representative to be used in Tier 3 testing as was used in Tier 2 testing or may select a different member or members of the group to represent the group in the Tier 3 tests.

(2) In addition to the criteria specific to particular tests as summarized and detailed in the testing guidelines (§§79.62 through 79.68), EPA may consider a number of factors (including, but not limited to):

(i) The number of positive and negative outcomes related to each endpoint;

(ii) The identification of concentration-effect relationships;

(iii) The statistical sensitivity and significance of such studies;

(iv) The severity of the observed effects (e.g., whether the effects would be likely to lead to incapacitating or irreversible conditions);

(v) The type and number of species included in the reported tests;

(vi) The consistency and clarity of apparent mechanisms, target organs, and outcomes;

(vii) The presence or absence of effective health test control data for base-fuel-only versus additive/base fuel mixture comparisons;

(viii) The nature and amount of known toxic agents in the emissions stream; and

(ix) The observation of lesions which specifically implicate inhalation as an important exposure route.

(3) Consideration of exposure. EPA retains discretion to consider, in addition to available toxicity data, any Tier 1 data on potential exposures to emissions from a particular fuel or fuel additive (or group of fuels and/or fuel additives) in determining whether to require Tier 3 testing. EPA may consider, but is not limited to, the following factors:

(i) Types and emission rates of speciated emission components;

(ii) Types and emission rates of combinations of compounds or elements of concern;

(iii) Historical and/or projected production volumes and market distributions; and

(iv) Estimated population and/or environmental exposures obtained through extrapolation, modeling, or literature search findings on ambient, occupational, or epidemiological exposures.

(b) Notice. (1) EPA will determine whether Tier 3 testing is necessary upon receipt of a manufacturer's (or group's) submittal as prescribed under §79.51(d). If EPA determines on the basis of the Tier 1 and 2 data submission and any other available information that further testing is necessary, EPA will require the responsible manufacturer(s) to conduct testing as described elsewhere in this section. EPA will notify the manufacturer (or group) by certified letter of the purpose and nature of any proposed testing and of the proposed deadline for completing the testing. A copy of the letter will be placed in the public record. EPA will provide the manufacturer a 60-day comment period after the manufacturer's receipt of such notice. EPA may extend the comment period if it appears from the nature of the issues raised that further discussion is warranted. In the event that no comment is received by EPA from the manufacturer (or group) within the comment period, the manufacturer (or group) shall be deemed to have consented to the adoption by EPA of the proposed Tier 3 requirements.

(2) EPA will issue a notice in the Federal Register of its intent to require testing under Tier 3 for a particular fuel or additive manufacturer and that a copy of the letter to the manufacturer outlining the Tier 3 testing for that manufacturer is available in the public record for review and comment.

The public shall have a minimum of thirty (30) days after the publication of this notice to comment on the proposed Tier 3 testing.

(3) EPA will include in the public record a copy of any timely comments concerning the proposed Tier 3 testing requirements received from the affected manufacturer or group or from the public, and the responses of EPA to such comments. After reviewing all such comments received, EPA will adopt final Tier 3 requirements by sending a certified letter describing such final requirements to the manufacturer or group. EPA will also issue a notice in the Federal Register announcing that it has adopted such final Tier 3 requirements and that a copy of the letter adopting the requirements has been included in the public record.

(4) Prior to beginning any required Tier 3 testing, the manufacturer shall submit detailed test protocols to EPA for approval. Once EPA has determined the Tier 3 testing requirements and approves the test protocols, any modification to the requirements shall be governed by §79.51(f).

(c) Carcinogenicity and Mutagenicity Testing. (1) A potential need for Tier 3 carcinogenicity and/or mutagenicity testing may be indicated if the results of the In vivo Micronucleus Assay, required under §79.64, the In vivo Sister Chromatid Exchange Assay, required under §79.65, the Salmonella mutagenicity assay required under §79.68, or relevant pathologic findings under §79.62 demonstrate a statistically significant dose-related positive response as compared with appropriate controls. Alternatively, Tier 3 carcinogenicity testing and/or mutagenicity testing may be required if there are positive outcomes for at least one concentration in two or more of the tests required under §§79.64, 79.65, and 79.68.

(2) The testing for carcinogenicity required under this paragraph may, at EPA's discretion, be conducted in accordance with 40 CFR 798.3300 or 798.3320, or their equivalents (see suggested references following each health effects testing guideline). The testing for mutagenicity required under this paragraph may likewise be conducted in accordance with 40 CFR 798.5195, 798.5500, 798.5955, 798.7100, and/or other suitable equivalent testing (see suggested references following each health effects testing guideline). EPA may supplement or modify guidelines as required to ensure that the prescribed testing addresses the identified areas of concern.

(d) Reproductive and Teratological Effects Testing. (1) A potential need for Tier 3 testing may be indicated if the results of the Fertility Assessment/Teratology study required under §79.63 or relevant findings under §79.62 demonstrate, in comparison with appropriate controls, a statistically significant dose-related positive response in one or more of the possible test outcomes. Similarly, Tier 3 testing may be indicated if statistically significant positive results are confined to either sex, or to the fetus as opposed to the pregnant adult.

(2) The testing for reproductive and teratological effects required under this paragraph may, at EPA's discretion, be conducted in accordance with 40 CFR 798.4700 and/or by performance of a reproductive assay by continuous breeding. These guidelines may be modified or supplemented by EPA as required to ensure that the prescribed testing addresses the identified areas of concern.

(e) Neurotoxicity Testing. (1) A potential need for Tier 3 neurotoxicity testing may be indicated if either the results of the Neuropathology Assessment required under §79.67 shows concentration-related effects in exposed animals or the Glial Fibrillary Acidic Protein Assay required under §79.66 demonstrates a statistically significant concentration-related positive response as compared with appropriate controls. Similarly, Tier 3 neurotoxicity testing may be indicated if relevant results under §79.62 demonstrate a statistically significant positive response in comparison to appropriate controls.

(2) The testing for neurotoxicity required under this paragraph may, at EPA's discretion, be conducted in accordance with 40 CFR 798.3260 and 40 CFR part 798 subpart G. These guidelines may be modified or supplemented by EPA as required to ensure that the prescribed testing addresses the identified areas of concern.

(f) General and Pulmonary Toxicity Testing. (1) A potential need for Tier 3 general and/or pulmonary toxicity testing may be indicated if, in comparison with appropriate controls, the results of the Subchronic Toxicity Study, pursuant to §79.62, demonstrate abnormal gross analysis or histopathological findings (especially as relates to lung pathology from whole-body preserved test animals) or persistence or delayed occurrence of toxic effects beyond the exposure period.

(2) A potential need for Tier 3 testing with respect to other organ systems or endpoints not addressed by specific Tier 2 tests, e.g., hepatic, renal, or endocrine toxicity, may be demonstrated by findings in the Tier 2 Subchronic Toxicity Study (pursuant to §79.62) or by findings in the Tier 1 literature search of adverse functional, physiologic, metabolic, or histopathologic effects of fuel or

additive emissions to such other organ systems or any other information available to EPA. In addition, findings in the Tier 1 emission characterization of significant levels of a known toxicant to such other organ systems and endpoints may also indicate a need for relevant health effects testing. The testing required under this paragraph may include tests conducted in accordance with 40 CFR 798.3260 or 798.3320. These guidelines may be modified or supplemented by EPA as necessary to ensure that the prescribed testing addresses the identified areas of concern.

(3) The testing for general/pulmonary toxicity required under this paragraph may, at EPA's discretion, be conducted in accordance with 40 CFR 798.2450 or 798.3260. These guidelines may be modified or supplemented by EPA as necessary to ensure that the prescribed testing addresses the identified areas of concern. Pulmonary function measurements, host defense assays, immunotoxicity tests, cell morphology/morphometry, and/or enzyme assays of lung lavage cells and fluids may be specifically required.

(g) Other Tier 3 Testing. (1) A manufacturer or group may be required to use up-to-date modeling, sampling, monitoring, and/or analytic approaches at the Tier 3 level to provide:

(i) Estimates of exposures to the emission products of a fuel or fuel additive or group of products;

(ii) The expected atmospheric transformation products of such emissions; and

(iii) The environmental partitioning of such emissions to the air, soil, water, and biota.

(2) Additional emission characterization may be required if uncertainty over the identity of chemical species or rate of their emission interferes with reasonable judgments as to the presence and/or concentration of potentially toxic substances in the emissions of a fuel or fuel additive. The required tests may include characterization of additional classes of emissions, the characterization of emissions generated by additional vehicles/engines of various technology mixes (e.g., catalyzed versus non-catalyzed emissions), and/or other more precise analytic procedures for identification or quantification of emissions compounds. Additional emissions testing may also be required to evaluate concerns which may arise regarding the potential effects of a fuel or fuel additive on the performance of emission control equipment.

(3) A manufacturer or group may be required to conduct biological and/or exposure studies at the Tier 3 level to evaluate directly the potential public welfare or environmental effects of the emissions of a fuel or additive, if significant concerns about such effects arise as a result of EPA's review of the literature search or emission characterization findings in Tier 1 or the results of the toxicological tests in Tier 2.

(4) With regard to group submittals, Tier 3 studies on a fuel or additive product(s) other than the originally specified group representative may be required if specific differences in the product's composition indicate that its emissions may have different toxicologic properties from those of the original group representative.

(5) Additional emission characterization and/or toxicologic tests may be required to evaluate the impact of different vehicle, engine, or emission control technologies on the observed composition or health or welfare effects of the emissions of a fuel or additive.

(6) Toxicological tests on individual emission products may be required.

(7) Upon review of information submitted for an aerosol product under §79.58(e), emissions characterization, exposure, and/or toxicologic testing at a Tier 3 level may be required.

(8) A manufacturer which qualifies for and has elected to use the special provisions for the products of small businesses (pursuant to §79.58(d)) may be required to conduct emission characterization, exposure, and/or toxicologic studies at the Tier 3 level for such products, as specified in §79.58(d)(4).

(9) The examples of potential Tier 3 tests described in this section do not in any way limit EPA's broad discretion and authority under Tier 3.