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# Appendix: Alternative Tier 2 health effects testing requirements for gasoline and oxygenated gasolines

The Clean Air Act (CAA), among other things, gives the Environmental Protection Agency (EPA) authority and primary responsibility to assure that the use of automotive fuels and fuel additives does not present an undue health risk to the general public. If there are not sufficient data to make such a determination, the CAA also provides EPA the ability to require that responsible companies generate the necessary information. The CAA, as amended, requires the Administrator of EPA to promulgate regulations requiring manufacturers of designated fuel and fuel additives (F/FAs) to register their products with EPA prior to introduction into commerce and to conduct tests to determine potential health effects of such products. These regulations can be found at 40 CFR Part 79. They include regulations that established health effects testing requirements for the registration of designated F/FAs as authorized by sections 211(b) (2) and 211(e) of the CAA (40 CFR, 1994).

The F/FA health effects testing requirements are organized within a three-tier structure. Tier 1 requires F/FAs manufacturers to provide EPA (1) the identity and concentration of emissions products of designated F/FAs, and (2) any available information regarding the health and welfare effects of certain whole and speciated emissions (40 CFR 79.52). Tier 2 requires F/FAs manufacturers to test each F/FA for subchronic systemic and organ toxicity, as well as the assessment of specific health effects endpoints (40 CFR 79.53). Tier 3 testing may be required, at EPA's discretion, when remaining uncertainties as to the significance of observed health or welfare effects, or emissions exposures interfere with EPA's ability to reasonably assess the potential risks posed by emissions from a F/FA (40 CFR 79.54). EPA's regulations also permit submission of adequate existing test data in lieu of conducting new tests that could be duplicative (40 CFR 79.53(b)). In addition, EPA's regulations permit health effects testing requirements to be satisfied by participation in groups that are established in accordance with the grouping criterion set forth at 40 CFR 79.56. The regulations also include provisions for small businesses and certain types of products (40 CFR 79.58). For example, manufacturers with total annual sales that are below certain threshold levels are exempt from Tier 2 or both Tiers 1 and 2 testing requirements.

At EPA's discretion, the standard Tier 2 health effects testing requirements for a designated F/FA (or group thereof) maybe modified by substituting, adding, or deleting testing requirements; or changing the underlying vehicle or engine specifications (40 CFR 79.58(c)). EPA will not, however, delete a testing requirement for a specific endpoint in absence of either existing adequate information or an alternative testing requirement for that endpoint (40 CFR 79.58(c)). When EPA exercises its authority under this provision, it will allow an appropriate time for completion of the prescribed alternative tests.

Finally, the introduction into commerce of F/FAs that are not substantially similar to any F/FA used in vehicle or engine emissions certification is prohibited, unless granted a waiver pursuant to section 211(f)(4) of the Act.

Beginning in 1990, EPA became cognizant of several expert analyses that demonstrated the necessity for baseline gasoline and oxygenates health effects testing. They included a committee of the National Science and Technology Council that reviewed published and unpublished reports made available since 1990). This committee identified the following areas in an Interagency Assessment as requiring additional research: human exposures, pharmacokinetics of MTBE; acute health effects related to oxygenates, mechanisms of carcinogenicity; and dose–response relationships between exposure to oxygenates and risk of carcinogenicity (NSTCC, 1997). Similarly, the Health Effects Institute for Oxygenates Evaluation Committee conducted an intensive review of the existing oxygenates health effects database, EPA risk assessments, and health effects of new oxygenates as they relate to other pollutants whose emissions are altered by use of oxygenates. The Oxygenate Evaluation Committee identified the following outstanding research needs: personal exposures to oxygenates using standard protocols, metabolism of MTBE; pharmacokinetics of other ethers; short-term effects using controlled human exposures; neurotoxic effects, neoplastic and non-neoplastic long-term effects; studies on the genotoxicity of MTBE; developmental effects, and assessment of potential contamination of drinking water with MTBE (Health Effects Institute, 1996). Additionally, a Committee of the National Research Council reviewed the Interagency Assessment and identified the following research needs: representative personal exposure monitoring of MTBE in the exposed population; toxicokinetic data of MTBE and other oxygenates; study of exposure to MTBE and acute health effects; and potential for biodegradation of MTBE and other alkyl ether oxygenates in surface water, soil and groundwater (National Research Council, 1996). The expert analyses clearly demonstrated this necessity for testing focusing on acute health effects, exposure assessments, pharmacokinetic parameters, and potential exposures via drinking water. EPA concluded in a review of the Interagency Assessment and the Health Effects Institute Review: "It is quite evident, however, that a consistent theme in all the reports is a need for more information on the exposure and health aspects of conventional and oxygenated fuels" (EPA, 1996).

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On August 20, 1997, EPA notified the American Petroleum Institute (API) test group consortium (hereinafter the Section 211(b) Research Group) of proposed Alternative Tier 2 health effects testing requirements for baseline gasoline and baseline gasoline containing methyl tertiary butyl ether (MTBE) and oxygenated non-baseline gasolines, and the proposed schedule for completion and submission of such tests. The consortium comprised manufacturers of gasoline with or without the fuel additive MTBE, ethyl tertiary butyl ether (ETBE), ethyl alcohol (EtOH), tertiary amyl methyl ether (TAME), diisopropyl ether (DIPE), and tertiary butyl alcohol (TBA) and manufacturers of these oxygenates and other gasoline additives. An associated Federal Register notice (62 FR 474000) initiated a 60-day public comment period, which was extended an additional 60 days (62 FR 60675), to accommodate both the Section 211(b) Research Group's request for an extension, and to also allow the general public additional time to provide comments. On November 2, 1998, EPA notified the Section API 211(b) Research Group of the specific tests required under the Alternative Tier 2 provisions, under the F/FA health effects testing requirements of 40 CFR 79 (Subpart F), for baseline gasoline and oxygenated non-baseline gasolines, and the schedule for completion and submission of such tests. A copy of the final notification letter as well as the tests and schedule under the Alternative Tier 2 provisions were placed in the Public Docket Number A-96–16 (EPA, 1998). On December 9, 1998, the Agency published a notice announcing that EPA had notified the Section 211(b) Research Group of the final Alternative Tier 2 health effects testing requirements under 40 CFR 79.58(c) (63 FR 67877).

In accordance with 40 CFR 79.56(a), manufacturers of F/FAs were permitted to satisfy the Alternative Tier 2 testing requirements on a group basis. Group representatives were formed in accordance with 40 CFR 79.56(e)(4)(i)(A). Each individual manufacturer that was a member of such a group, however, was individually subject to the testing and data submission requirements unless otherwise exempt under certain provisions of 40 CFR 79. The baseline gasoline group was represented by the Gasoline Base Fuel specified in 40 CFR 79.55(b). Each oxygenate-gasoline group was represented by a formulation comprised of the oxygenate in question (chemical grade or better) mixed in the Gasoline Base Fuel (as specified in Section 79.55(b)) to achieve the following volume percent: Methyl Tertiary Butyl Ether (15 volume percent), Ethyl alcohol (10 volume percent), Ethyl Tertiary Butyl Ether (17 volume percent), Tertiary amyl methyl ether (17 volume percent), Di-isopropyl ether (17 volume percent), and Tertiary butyl alcohol (12 volume percent). For the purposes of conducting inhalation exposure studies, the provisions of 40 CFR 79.53(c)(1) applied. The F/FA program guidelines for Good Laboratory Practices (GLP), as provided at 40 CFR 79.60 were in effect for purposes of the entire testing regimen. The provisions of 40 CFR 79.61 were used for purposes of conducting the inhalation exposure studies. Detailed, written, and where applicable, peer-reviewed protocols were developed by the 211(b) Research Group and approved by EPA prior to the initiation of any of the required Alternative Tier 2 inhalation exposure studies. Where applicable, the objectives and methods for performing assessments were conducted in accordance with relevant provisions of the Health Effects Test Guidelines (Pt. 870) published by the Office of Prevention, Pesticides and Toxic Substances (OPPTS) (Docket Item A-96–16/II-1). For further information on the specific requirements and objective of this test program, please refer to the final notification letter[5] and the public record (Federal Docket, 2003).

The Alternative Tier 2 testing regimen contrasts with the standard Tier 2 requirements, which may require testing of both evaporative and combustion emissions because toxicological studies were based on animal exposures to only evaporative emissions mixtures of baseline gasoline or an oxygenated fuel that is blended into the baseline gasoline in question. The decision to focus on evaporative emissions exposure studies only was based in part on peer-reviewed arguments presented by the Section 211(b) Research Group. As a result of an API-sponsored information meeting on December 11 and 12, 1995, toxicological experts presented analysis demonstrating that relatively high concentrations of carbon monoxide (CO) in gasoline exhaust imposed a practical limit on achievable exposures to hydrocarbon (HC) exhaust components. General agreement was reached among peer-reviewed experts in the field of toxicological testing that the amount of exhaust gas dilution required to avoid CO toxicity of animal subjects would bring the concentration of HCs in the exposure chamber below the no-effect level. At that time, it was concluded that further exhaust emission toxicological tests of gasoline-based F/FAs would not produce meaningful results. At that time also, EPA scientists generally concurred that further inhalation toxicological testing of gasoline-based combustion emissions, if conducted using the approach described in the F/FA rule, seemed unlikely to provide additional useful data for a comparative risk assessment. Their concurrence was based on the likelihood that, at the exhaust dilution ratios necessary to avoid acute CO toxicity, the effects of the inhaled combustion mixture would be dominated by exposure to CO and/or oxides of nitrogen (NOx) rather than by HCs of primary interest. This concurrence did not, however, provide a resolution of either cancer or non-cancer health risks of gasoline (or oxygenated fuel) combustion emissions. On the contrary, the reviewing EPA scientists recommended continued evaluation of other approaches for investigating gasoline exhaust toxicity, such as the use of synthesized surrogate exhaust mixtures, the use of different exposure routes, and/or development of analytical models to assess comparative risks.

In sum, the general objectives of this test program were threefold. (1) Develop a comprehensive characterization of the toxicological effects in test animals of inhalation exposures to evaporative emissions of Baseline Gasoline and (separately) MTBE-gasoline; (2) determine potential dose–response relationships and No Observed Adverse Effects Levels (NOAELs) for specific toxicological endpoints; and (3) together with information from related studies on human population exposure levels, this information should permit accurate quantitative comparisons of the relative toxicological risks of baseline gasoline and MTBE-oxygenated fuels blended into baseline gasoline, as well as providing a solid basis for comparison with other oxygenate-gasoline fuel formulations. The required assessments included basic inhalation toxicity in the context of a subchronic exposure, as well as tests to determine potential reproductive, developmental, neurotoxic, immunotoxic, mutagenic, and carcinogenic (chronic exposure) effects.

Thus, the Alternative Tier 2 testing program was not intended to address every identified research need on baseline gasoline and the various oxygenated fuels blended into baseline gasoline. Rather, the test program was intended to fill critical gaps and act as a screen to determine the need for additional information that may be necessary to enable the Agency to make decisions concerning the potential risks associated with these F/FAs. EPA believed, however, at the time of requiring this testing program that the public interest would be best served by timely initiation of appropriate toxicity testing on the evaporative emissions of baseline gasoline and certain oxygenated fuels blended into baseline gasoline while the Agency continued to evaluate the complex issues surrounding exhaust emissions testing. EPA received no public comments disagreeing with this approach. EPA also recognized that the results of evaporative emissions tests, together with information on human population exposures to various evaporative and combustion emissions components, may change current perceptions about the continued need for, and specific targets of, future combustion emissions studies. Potential requirements to investigate the

toxicity of combustion emissions would be reconsidered at the Tier 3 level.

Consistent with the general strategy of the F/FA testing program, the Alternative Tier 2 testing regimen was part of a tiered approach, which may also include future Tier 3 test requirements. Such a stepwise approach helps to ensure a wise investment of manufacturer and laboratory resources. It also allows the Alternative Tier 2 results to influence the objectives and design of any necessary follow-up studies at the Tier 3 level. Changes in the F/FA usage pattern over time may also alter future research priorities. Furthermore, some information gaps may be filled by other studies currently being conducted; conversely, research work that EPA understands to be either ongoing or planned may not be done after all, may be inadequately performed, or may raise important new concerns that must be evaluated. Thus, the Alternative Tier 2 requirements must be regarded as the first step in a test regimen, which may encompass one or more additional steps at the Tier 3 level.

## References

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