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Editorial

Introduction: Gasoline health effects and risk management

In 1994 the U.S. Environmental Protection Agency (EPA) issued a final rule under the Clean Air Act (CAA) requiring new health effects information and testing for motor vehicle fuels and fuel additives. The rule, referred to as the "211(b)" rule, directed producers of motor vehicle fuels and fuel additives to provide information on the composition of emissions from their products and the potential effects of these emissions on the public health and welfare. To fulfill these requirements, the American Petroleum Institute (API) organized the 211(b) Research Group, an unincorporated group of over two hundred fuel, oxygenate, and fuel additive manufacturers, which embarked upon a nearly 20 year effort to fulfill the requirements of the rule.

This issue of Regulatory Toxicology and Pharmacology is devoted to describing the 211(b) rule requirements, the petroleum industry's response, and the results of toxicity studies on evaporative emissions. This was by no means the first effort to characterize the hazards of gasoline. The first article in the supplement "**Gasoline Toxicology: Overview of Regulatory and Product Stewardship Programs**" (Swick et al., 2014a) describes other mandatory and voluntary product stewardship and toxicology testing programs that have generated hazard characterization data for gasoline, the refinery process streams used to blend gasoline, and some of the individual chemical constituents of gasoline.

A major challenge was how to safely and correctly produce samples of the individual substances to be tested. The second paper in this issue "**Health Assessment of Gasoline and Fuel Oxygenate Vapors: Generation and Characterization of Test Materials**" (Henley et al., 2014) describes the extensive research involved in designing a method to generate the evaporative emissions used in these toxicology studies. Due to the extreme flammability of gasoline, it was not a trivial effort to develop and maintain safe handling procedures at several contract laboratories to ship, store and perform studies with the test articles. The 211(b) Rule required the construction of specialized equipment at each laboratory, operated under strict conditions of temperature and evaporated volume. Those conditions imposed significant logistical and safety issues which led the Research Group to undertake development of an improved method for the generation of test substances. The paper provides details of the fuels evaluated in the testing program, and of the generation and characterization of the test materials designed to mimic real-world human exposures. It also describes GLP-compliant analytic procedures developed to monitor atmospheric exposures in the animal studies and to ensure reproducible exposures at multiple contract laboratories.

The following papers in this issue summarize and compare the results of the toxicology studies on the evaporative emission substances. These studies assessed whether oxygenates added to gasoline influences potential hazard of the evaporative emissions to which humans may be exposed. All of these studies conformed to EPA guidelines where available, and where none existed, the Research Group worked with academic and government experts to develop sound experimental approaches to meet or exceed the requirements of the 211(b) rule. This series of studies "**Health Assessment of Gasoline and Fuel Oxygenate Vapors**" includes the following:

Sub-chronic Inhalation Toxicity (Clark et al., 2014) relates the results in Sprague–Dawley rats of seven separate inhalation studies of baseline gasoline vapor condensate or vapor condensate from gasoline blended with different oxygenates. These studies also served as the main exposure studies for three separate satellite groups assessing genetic toxicity, neurotoxicity, and immunotoxicity. Their conclusions are described in the following three papers:

Micronucleus and Sister Chromatid Exchange Evaluations – used the bone marrow micronucleus test to identify chromosome damage and aneuploidy, and the sister chromatid exchange test (SCE) to detect reciprocal exchanges of DNA between homologous loci of two sister chromatid strands of a duplicating chromosome (Schreiner et al., 2014).

Neurotoxicity Evaluation – used standard neurotoxicity screening batteries as well as analysis of glial fibrillary acidic protein (GFAP) in the brain. The GFAP assay was performed in Dr. O'Callaghan's laboratory as no commercial laboratories were sufficiently experienced to perform this assay. The results demonstrated that the GFAP assay is probably not effective for evaluating petroleum hydrocarbon materials. (O'Callaghan et al., 2014).

Immunotoxicity Evaluation – used antibody-forming cell (AFC) response to the T-dependent antigen, sheep erythrocyte (sRBC) to determine the effects on the humoral components of the immune system (White et al., 2014).

Following those articles are the results of three studies which investigated the reproductive and developmental toxicity of the same gasoline and gasoline/oxygenate vapor condensates used in the sub-chronic toxicity studies:

Reproductive Toxicity – used a two generation protocol design in Sprague Dawley rats and also used the GFAP assay to assess neurotoxicity (Gray et al., 2014).

Developmental Toxicity in Mice – evaluated the maternal and developmental toxicity in CD-1 mice of both gasoline and gasoline blended with MTBE (Roberts et al., 2014a).

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Developmental Toxicity in Rats – evaluated the maternal and developmental toxicity in Sprague–Dawley rats of gasoline and gasoline blended with six different oxygenates (Roberts et al., 2014b).

Other novel aspects of the testing program included the use of external experts to provide peer review of the laboratory reports. Special thanks are owed to Drs. Richard Schlesinger, Thomas Goldsworthy, and James Bond for their review and guidance. The Research Group also contracted with independent quality assurance experts to audit both the laboratories and the study reports in addition to the QA procedures of the laboratory.

As to the future of gasoline toxicology and regulation, the Research Group has completed all of the hazard screening studies required in the 211(b) rule which demonstrate a low potential for hazard from evaporative emissions encountered by the public when refueling vehicles. Exposure assessment studies separately conducted and reported as part of compliance with the 211(b) rule (Zielinska et al., 2012), demonstrate a wide margin of safety between various high-end exposure scenarios and the no observed adverse effect levels (NOAEL) demonstrated in the hazard screening studies reported in this issue. In addition, post-1994 fuel and vehicle regulations have continued to decrease exposure to gasoline vapor and exhaust emissions (e.g. reduced vapor pressure, sulfur, and benzene in the fuel; on-board refueling vapor canisters in cars; strict specifications on portable gas cans; more stringent tailpipe emission standards, etc.). The final article in this issue, "**Gasoline Risk Management: A Compendium of Regulations, Standards, and Industry Practices**" (Swick et al., 2014b), summarizes those regulations which provide the U.S. federal government extensive authority to regulate the entire gasoline lifecycle—from manufacture, through distribution, to end-use—all of which are subject to detailed, complex, and overlapping regulatory schemes intended to protect human health, welfare, and the environment. The article also describes the broad array of voluntary standards and best management practices implemented by industry to ensure that risks from gasoline manufacturing, distribution, and use are minimized.

For those interested in additional detail on the 211(b) rule, the appendix to this supplement, "**Alternative Tier 2 Health Effects Testing Requirements for Gasoline and Oxygenated Gasolines**" describes the events and expert analyses leading up to the development of the rule, the tiered structure of the requirements, what specific testing was required, and the overall objectives of the program. Also discussed, are the publication of the proposed rule and the subsequent public comment period, and the changes made to the final rule in acknowledgment of already existing data and laboratory safety concerns.

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