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Gasoline toxicology: Overview of regulatory and product stewardship programs

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ABSTRACT

Significant efforts have been made to characterize the toxicological properties of gasoline. There have been both mandatory and voluntary toxicology testing programs to generate hazard characterization data for gasoline, the refinery process streams used to blend gasoline, and individual chemical constituents found in gasoline. The Clean Air Act (CAA) (Clean Air Act, 2012: § 7401, et seq.) is the primary tool for the U.S. Environmental Protection Agency (EPA) to regulate gasoline and this supplement presents the results of the Section 211(b) Alternative Tier 2 studies required for CAA Fuel and Fuel Additive registration. Gasoline blending streams have also been evaluated by EPA under the voluntary High Production Volume (HPV) Challenge Program through which the petroleum industry provide data on over 80 refinery streams used in gasoline. Product stewardship efforts by companies and associations such as the American Petroleum Institute (API), Conservation of Clean Air and Water Europe (CONCAWE), and the Petroleum Product Stewardship Council (PPSC) have contributed a significant amount of hazard characterization data on gasoline and related substances. The hazard of gasoline and anticipated exposure to gasoline vapor has been well characterized for risk assessment purposes.

1. Introduction

Gasoline is a liquid hydrocarbon fuel that is used in spark ignition engines for automobiles, tractors, lawn-mowers, snowmobiles, jet skis, and dozens of other types of equipment. Modern gasoline, the focus of this review, is the result of significant evolution over the past century. Improvements in refining practices, engine design, and better understanding of the health and environmental impacts have all worked to create the version of gasoline now on the market. Many of these design and manufacturing improvements either resulted in, or were the result of, a wide range of standards and regulations to ensure a high level of product consistency in the marketplace, which is essential given the complexity of modern engines.

In the U.S., gasoline is a blended product (i.e., mixture), which is not listed on the Toxic Substances Control Act (TSCA) Chemical Inventory. However, the substances that are used to blend gasoline – such as refinery process streams – are on the TSCA Inventory (API, 1983; USEPA, 1995a). In the European Union (EU), gasoline is an unique substance on the EU Chemical Inventory (ESIS, 2014) and is identified by the Chemical Abstract Service (CAS) registry number "86290-81-5," the CAS name "Gasoline," and the CAS definition "A complex combination of hydrocarbons consisting primarily of paraffins, cycloparaffins, and, aromatic and olefinic hydrocarbons having carbon numbers predominantly greater than C3 and boiling in the range of 30–260 °C (86–500°F)."

Whether defined as a substance or a mixture, gasoline is blended from various refinery process streams to achieve the required physical property, performance, and composition specifications. Gasoline typically contains several hundred individual hydrocarbon constituents in the C4–C12 carbon-range and several additives in the part-per-million (ppm) concentration range that prevent fuel degradation (i.e., antioxidant, metal deactivator) or improve engine performance (i.e., detergent) (ASTM, 2010). The refinery streams that comprise the bulk of the gasoline volume are in a class of substances referred to as **U**nknown or **V**ariable compositions, **C**omplex reaction products and **B**iological (UVCB) substances (USEPA, 1995b).

There have been both mandatory and voluntary testing programs to generate hazard characterization data on gasoline and refinery process streams. The Clean Air Act (CAA) (Clean Air Act, 2012: § 7401, et seq.) provides the U.S. Environmental Protection

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Agency (EPA) the authority to regulate emissions of gasoline. The wide scope of that authority is reviewed in detail elsewhere in this supplement (Swick et al., 2014). The specific authority under CAA Section 211 (Clean Air Act, 2012: § 211) is reviewed in this paper. EPA also has authority under the Toxic Substances Control Act (TSCA) (Toxic Substances Control Act, 2012: § 2601, et seq.) to require hazard screening tests under Section 4. Several instances of test rules for gasoline components issued under TSCA Section 4 are reviewed in this paper. EPA also initiated a voluntary program asking industry to develop and make publically available data on high production volume (HPV) chemicals (USEPA, 1998). HPV chemicals are those substances that are manufactured or imported into the U.S. in amounts exceeding one million pounds per year. Virtually all refinery process streams used to make gasoline meet this criterion for HPV chemicals.

EPA also initiated the Voluntary Children's Chemical Evaluation Program (VCCEP) in December 2000 to assess the risks associated with potential children's exposure to approximately 20 large volume chemicals. Industry funded the data collection and an independent panel conducted the review. Four of the chemicals reviewed in the VCCEP program are constituents in gasoline: benzene, toluene, ethylbenzene, and xylenes (BTEX).

Product stewardship efforts by individual companies and by industry trade associations have also contributed significantly to the available hazard characterization data on gasoline, its blending streams, and various chemical constituents. The American Petroleum Institute (API) and the European organization CONCAWE (Conservation of Clean Air and Water Europe) have also conducted studies on various petroleum products including gasoline. Another organization is the Total Petroleum Hydrocarbon Criteria Working Group (TPHCWG), which was formed as a coalition of industry and government groups to establish appropriate soil clean-up levels after spills of petroleum products like gasoline, jet fuel, diesel fuel, etc. The Petroleum Product Stewardship Council (PPSC) comprised of toxicologists from AMOCO, ARCO, BP, Chevron, Mobil, Texaco, and Unocal conducted hazard characterization studies on the blending streams used in gasoline and diesel fuels. Individual companies have also conducted and published relevant hazard studies on gasoline blending streams.

These regulatory and product stewardship efforts are described in more detail below, with the goal of providing references for the numerous reports and peer-reviewed publications that have resulted from that activity.

2. Gasoline studies mandated by the Clean Air Act

Section 211 of the Clean Air Act (CAA) gives the U.S. Environmental Protection Agency (EPA) broad authority to regulate the content and characteristics of gasoline and gasoline additives (Clean Air Act, 2012: § 7545). EPA's information requirements to obtain registration to sell fuel and fuel additives are quite strict and follow a three-tiered approach. (See Fig. 1).

2.1. 211(b) Research Group

In response to the tiered registration requirements, the American Petroleum Institute (API) organized the 211(b) Research Group (Research Group). The Research Group is an unincorporated group of fuel, fuel oxygenate, and fuel additive manufacturers affiliated by contractual obligation to meet the Tier 1 and Tier 2 testing requirements of Sections 211(b)(2) and 211(e) of the Clean Air Act (Clean Air Act, 2012: §§ 211(b)(2) and 211(e)). EPA has not yet initiated any Tier 3 actions under the rule.

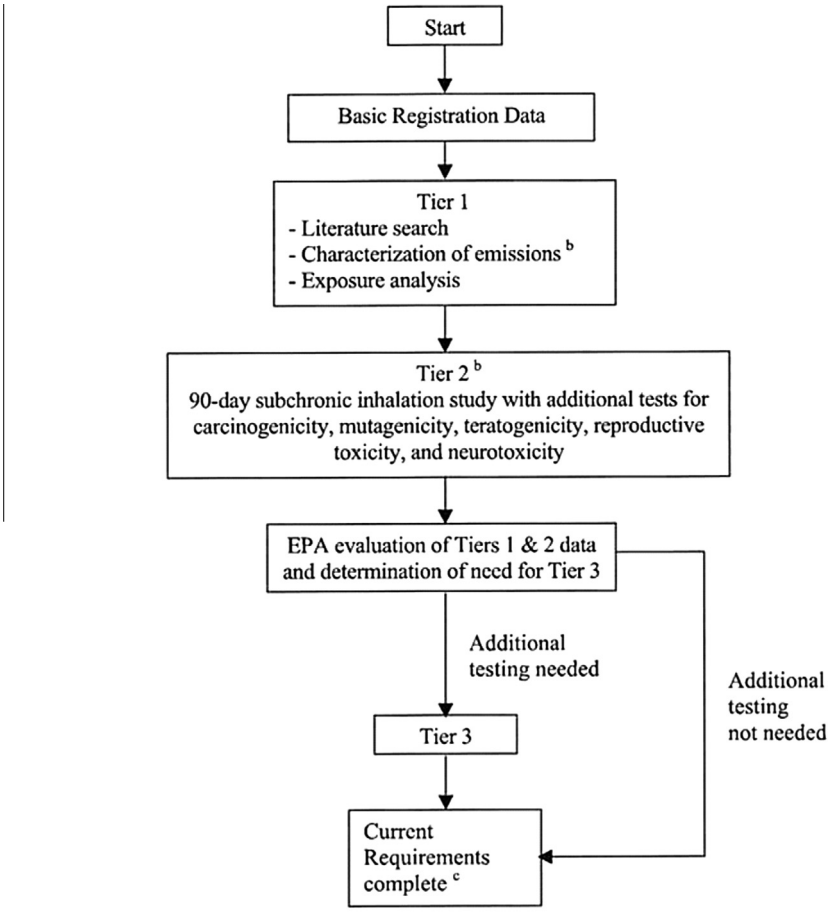
The 211(b) Research Group's purpose was to address two of the three categories of fuel outlined in the 211(b) Rule (Registration of Fuels and Fuel Additives, 2013: § 79.56). The Research Group tested: (1) "baseline" fuel groups that contain no elements other than carbon, hydrogen, oxygen, nitrogen, and sulfur, and gasoline containing less than 1.5% oxygen by weight, and diesel containing less than 1.0% oxygen; and (2) "non-baseline" fuel groups that contain only the elements listed above, but are either derived from nonconventional sources of oil, or contain in excess of 1.5% or 1.0% oxygen by weight for gasoline and diesel, respectively. Oxygenates in non-baseline fuel groups tested by the Research Group were ethanol (EtOH), tertiary-butyl alcohol (TBA), methyl tertiary-butyl ether (MTBE), ethyl tertiary-butyl ether (ETBE), tertiary-amyl methyl ether (TAME), and di-isopropyl ether (DIPE). The Research Group's testing scope does not include a third category of fuel groups, namely atypical fuel groups, which consist of fuels or fuel additives that contain elements other than carbon, hydrogen, oxygen, nitrogen, and sulfur.

2.2. Section 211(b) Tier 1 Fuel and Fuel Additives Hazard Characterization Program

Tier 1 requirements included a literature search of available studies for health and welfare effects of substances in diesel exhaust, gasoline exhaust, and gasoline evaporative emissions. To help fulfill these requirements, the Research Group contracted with EA Engineering, Science & Technology, Inc. to conduct this search. Twelve bibliographic databases were selected for searching on the basis of content, scope, and relevancy to this effort. Databases were searched back either 30 years or to their origins for information on health or welfare effects on the following emission entities: diesel fuel exhaust, gasoline evaporative emissions, and gasoline exhaust, as the three whole (primary) emissions; select fractions or classes of compounds (16) associated with these emissions (ethers, alcohols, hydrocarbons, ketones, and aldehydes as "speciated emissions" along with 11 select naphtha fractions); and numerous individual chemicals (173) found in these three primary emissions. For select chemicals (approximately 20) having enormous information bases in the open literature, comprehensive reviews were used to identify prior relevant studies, with literature searches providing information on more recent, post-review studies. Unpublished studies provided by Research Group member companies were also reviewed. Information from studies identified as relevant and appropriate was then extracted to summary tables (up to 15 combined health and welfare effects tables may exist per chemical or whole emission) for a wide variety of health or welfare effects. Study summaries were organized into a single report and submitted to EPA (EA Engineering, 1997) along with completed copies of the articles/studies.

To further fulfill Tier 1 requirements, the Research Group contracted with Southwest Research Institute to conduct vehicle emissions testing for the gasoline baseline and non-baseline fuels/fuel additives (F/FAs), and to conduct a literature review to characterize diesel exhaust emissions from heavy-duty vehicles.

For the gasoline F/FAs, exhaust and evaporative emission measurements were conducted using a 1996 Toyota Camry operating on a baseline ("industry average," RF-A) gasoline and six gasoline fuels each splash blended with specific oxygenates (EtOH, MTBE, ETBE, TAME, TBA, and DIPE). The exhaust emissions portion of the test matrix consisted of triplicate Federal Test Procedure (FTP) emissions tests with the vehicle operating in each of three different configurations. The three configurations included: (1) original equipment manufacturer's configuration; (2) without catalytic converter; and (3) without evaporative emission canister. One-hour diurnal heat build and hot-soak loss evaporative emission tests were conducted for test configurations 1 and 3 (Research Group, 1997).



[a] This chart shows the general requirements for most F/FAs, and do not take into account any special provisions which may apply.
[b] Required unless adequate data exist.
[c] EPA retains the authority to require additional testing if new concerns arise.

Fig. 1. Overview of Evaluation Tiers[a].

For diesel F/FAs, an in-depth literature search concluded that sufficient data exist in the public domain to meet the requirements for the characterization of exhaust emissions from heavy-duty diesel vehicles under 40 CFR, Part 79 (Registration of Fuels and Fuel Additives, 2013: § 79.52) (Research Group, 1996).

2.3. Section 211(b) Tier 2 Fuel and Fuel Additives Hazard Characterization Program

For Tier 2, the original 211(b) Rule required health effects testing in rodents on diesel and gasoline engine exhaust emissions, as well as on gasoline evaporative emissions. The Research Group sought to modify the final rule in each of these areas due to complications with performing such tests. The Research Group sponsored research and several literature reviews that were used in comments to EPA for development of an Alternative Tier 2 testing program.

The Research Group felt there was adequate existing data on diesel exhaust for all the required endpoints (Research Group, 1996). EPA agreed and dropped that requirement from the Alternative Tier 2 Testing Program (EPA Docket, 1998a,b). The Research Group also believed there was no value in subjecting rodents to gasoline engine exhaust emissions because the carbon monoxide content of the exhaust would likely overwhelm any other exhaust components. The significant acute toxicity and lethality of carbon monoxide is well studied and these effects would obscure the effects of other exhaust components (Barter et al., 1996). EPA agreed and dropped the gasoline engine exhaust emissions testing requirement from the Alternative Tier 2 Testing Program (EPA Docket, 1998a,b).

The Research Group developed an alternative method for generating the test article used in the rodent toxicology studies to the one outlined in the original 211(b) Rule (Fuels and Fuel Additives Registration Regulations, 1994: 33,092). The original EPA method required the "evaporative emissions" test atmosphere to be generated from whole gasoline in situ at the toxicology testing laboratory. The Research Group developed and demonstrated an alternative method where the test article was fabricated at a central facility that was compositionally similar to equilibrium vapor at near maximum in-use temperatures (EPA Docket, 1997). EPA approved the Research Group's proposed methodology as part of their Alternative Tier 2 Rulemaking Program (EPA Docket, 1998a,b).

2.4. Alternative Tier 2 hazard characterization studies

Because of the widespread use of gasoline, exposure to total hydrocarbon vapor and individual constituents has been studied in occupational, consumer, and general population exposure situations (Clayton, 1993; NATLSCO, 1995; CONCAWE, 1997, 2009;

Zielinska et al., 2012). These studies have shown that consumer exposures to gasoline vapors or their components were typically at their highest concentrations during the refueling of vehicles. Exposure concentrations could reach 10–100 ppm total hydrocarbon vapor while refueling, particularly prior to the implementation of vapor recovery devices both within the automobile and the fuel pump. While these exposures were relatively high, they were of short duration, and generally only for the most volatile constituents of gasoline.

While many of the initial hazard characterization studies of gasoline were done with wholly vaporized gasoline (API, 1977, 1978; MacFarland et al., 1984), the requirements set forthin § 211(b) of the CAA (Clean Air Act, 2012: § 211(b)) are intended to evaluate risks associated with evaporative emissions. As a result, these early wholly vaporized gasoline studies were not very useful for the risk assessment of gasoline vapor exposure during refueling. The composition of the vapor emissions during refueling is very different than the composition of the full liquid gasoline (Furey and Nagel, 1986; Roberts et al., 2001; McKee et al., 2000; Henley et al., 2014). Whole gasoline may have constituents in the C_4–C_{12} carbon range, whereas the evaporative emissions from gasoline are predominantly greater than 80% in the C_4–C_6 range, and there are no constituents at all in the C_9–C_{12} range (Henley et al., 2014). The hazard characterization studies done for the CAA 211(b) Alternative Tier 2 regulations were all conducted using this evaporative test article that closely resembles the evaporative emissions experienced by consumers during refueling (Henley et al., 2014).

All of the hazard characterization studies required under the final Alternative Tier 2 Rule are shown in Table 1 (EPA Docket, 1998a,b). The program did not include toxicological studies of combustion emissions. The health endpoints included assessments for repeat dose toxicity (Clark et al., 2014), neurotoxicity (O'Callaghan et al., 2014), genotoxicity (Schreiner et al., 2014), immunotoxicity (White et al., 2014), developmental toxicity (Roberts et al., 2014a; Roberts et al., 2014b), reproductive toxicity (Gray et al., 2014), and chronic toxicity/carcinogenicity (Benson et al., 2011). The results from the hazard characterization studies conducted for the Alternative Tier 2 Rule are described in the papers included in this supplement and elsewhere. A public website is being created that will permit viewing of the reports submitted to EPA. The website address will be www.211bResearchGroup.org. They can also be accessed at Regulations.gov with Docket ID Number: EPA-HQ-OAR-2003-0065.

In addition, the Alternative Tier 2 Rule also included development of pharmacokinetic data on the pure oxygenates and a multi-city exposure study to characterize high-end exposures from vehicle exhaust and evaporative emissions. The Research Group submitted pharmacokinetic data on TAME, MTBE, and EtOH that were accepted by EPA as sufficient to meet the requirements of the Alternative Tier 2 Rule. Studies on ETBE and TBA are ongoing, and studies for DIPE are at the stage of report finalizing.

Exposure studies were conducted in Houston, Chicago, and Atlanta (Winter and Summer) to examine the impact of reformulated gasoline (with either MTBE or EtOH as the oxygenate) on exposure to mobile source air toxics during various high-end micro-environment exposures. The micro-environments that were evaluated were:

- In-Car on Congested Freeway
- In-Car in Urban Canyon
- In-Car while Refueling
- In-Car at Underground Garage
- In-Car at Toll Plaza
- In-Car in Roadway Tunnel
- Out-of-Car while Refueling
- Out-of-Car on Sidewalk
- Out-of-Car at Sidewalk/Bus Stop
- Out-of-Car at Surface Parking Lot
- Out-of-Car at Underground Garage
- Out-of-Car at Outdoor Toll Plaza
- In-Car Trailing High-Emitting Vehicles

The report was completed and accepted by EPA in 2009 (Section 211(b) Tier 2 High End Exposure Study of Conventional and Oxygenated Gasoline, March 25, 2009-recompiled on June 3, 2011). The key findings of the study have been published (Zielinska et al., 2012).

3. Other regulatory initiatives

The Environmental Protection Agency (EPA) under the Toxic Substances Control Act (TSCA) has broad authority "to prevent unreasonable risks of injury to health or the environment associated with the manufacture, processing, distribution in commerce, use, or disposal of 'chemical substances.'" (Toxic Substances Control Act, 2012: § 2601, et seq.). At the heart of TSCA is the requirement that manufacturers and importers of "new" chemical substances (i.e., substances not listed on the TSCA "Inventory") submit a premanufacture notice (PMN) to EPA at least 90 days prior to manufacture or import. EPA can require testing of the submitted substance, as a condition of approval of the PMN. As a mixture, gasoline is specifically exempted from the statutory definition of a "chemical substance," but all the blending components of gasoline are subject to the PMN requirements. Although gasoline, as a fuel, is primarily regulated under the CAA, gasoline and its constituents have been subjected to rigorous hazard testing and risk reviews under a number of EPA programs, including TSCA Section 4 testing, EPA's High Production Volume (HPV) Challenge, and the Voluntary Children's Chemical Evaluation Program (VCCEP).

3.1. TSCA

Section 4 of TSCA authorizes EPA to require manufacturers, importers, and processors to test certain substances and mixtures that the Agency believes may present an unreasonable risk to human health or the environment. EPA implements its authority under Section 4 by publishing "test rules" for specific substances, which describe the substance for which testing is required, the health or environmental effects to be tested, and other relevant information. In lieu of promulgating a formal test rule, EPA has frequently negotiated enforceable consent agreements (ECAs) with companies that volunteer to perform testing on certain chemicals (Procedures Governing Testing Consent Agreements and Test Rules, 2013: §§ 790.60–790.68). Pursuant to its TSCA § 4 authority, EPA negotiated ECAs with gasoline manufactures and processors for the development and submission of test data for methyl tertiary-butyl ether (MTBE), tertiary-amyl methyl ether (TAME) and the nine-carbon aromatic hydrocarbon fraction (C_9 fraction) used in gasoline blending.

EPA sought to collect test data on MTBE because of concerns about "widespread human exposure to low-level fugitive emissions of MTBE at gasoline pumps and the lack of chronic health effects information" (Testing Consent Order on Methyl Tertiary Butyl Ether and Response to the Interagency Testing Committee, 1988: 10,391). EPA also expressed concerns about MTBE contamination of ground water. A task force of several MTBE manufacturers worked through the Oxygenated Fuels Association to conduct and submit to EPA a series of studies on repeat-dose toxicity, cytogenetics, developmental toxicity, neurotoxicity, carcinogenicity, pharmacokinetics, and reproductive effects (USEPA, 2014a). Following receipt and review of the data, the project was closed and EPA has since taken no further action (EPA Docket OPPTS-42098).

Table 1
211(b) Rule Alternative Tier 2 testing matrix.

Endpoint/TA	Baseline gasoline	Gasoline with EtOH	Gasoline with TBA	Gasoline with MTBE	Gasoline with ETBE	Gasoline with TAME	Gasoline with DIPE
90-Day subchronic	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Neurotoxicity (histopath/motor activity)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Glial fibulary acidic protein in brain regions	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Immunotoxicity	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Micronucleus	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sister-chromatid exchange	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Developmental toxicity	Yes – 2 species	Yes – 1 species	Yes – 1 species	Yes – 2 species	Yes – 1 species	Yes – 1 species	Yes – 1 species
Reproductive toxicity	Yes – 2 generation	Yes – 1 generation	Yes – 1 generation	Yes – 2 generation	Yes – 1 generation	Yes – 1 generation	Yes – 1 generation
Chronic toxicity/carcinogenicity	Yes			Yes			
Pharmacokinetic data			Yes		Yes		Yes
High-end exposure screening study	Yes	Yes		Yes			

The results of those studies were later published (Bevan et al., 1997a,b; Bird et al., 1997; Daughtrey et al., 1997; Lington et al., 1997; McKee et al., 1997; Miller et al., 1997).

EPA also sought to collect test data on TAME because of similar concerns (Testing Consent Order for Tertiary Amyl Methyl Ether, 1995: 14,910). A task force of several TAME manufacturers worked through the American Petroleum Institute (API) to conduct and submit to EPA a series of studies on repeat-dose toxicity, cytogenetics, developmental toxicity, neurotoxicity, pharmacokinetics, and reproductive effects (USEPA, 2014f). Following receipt and review of the data, the project was closed and EPA took no further action (EPA Docket OPPTS-44643). The results of several of those studies were later published (Sumner et al., 2003a,b,c; Tyl et al., 2003; Welsch et al., 2003).

Concerned about possible consumer and occupational exposures to mixed ethyltoluenes (ET) and 1,2,4-trimethylbenzene (1,2,4-TMB), EPA issued a Section 4 Test rule directing producers and processors of C_9 aromatic hydrocarbons (CAS registry number 70693-06-0) produced from the refining of crude oil to test the substance for neurotoxicity, mutagenicity, developmental toxicity, and reproductive effects (Identification of Specific Chemical Substance and Mixture Testing Requirements; Ethyltoluenes, Trimethylbenzenes, and the C9 Aromatic Hydrocarbon Fraction, 1985: 20,662). The Agency did not require testing of environmental effects because it determined that the available data were adequate to predict that ET and 1,2,4-TMB "neither persisted nor accumulated in the environment in a sufficient quantity that would likely result in an unreasonable risk to the environment." API took the lead in responding to the EPA test order and sponsored studies addressing developmental toxicity, mutagenicity, neurotoxicity, and reproductive effects (USEPA, 2014b). As with the MTBE and TAME testing, EPA closed the project and took no further action (EPA Dockets OPPTS-44536 and 44513). The results of the studies were later published (Schreiner et al., 1989; McKee et al., 1990; Douglas et al., 1993).

EPA also issued a test rule on a related chemical, 1,3,5-trimethylbenzene (1,3,5-TMB or mesitylene) in 1993 requiring 14-day and 90-day repeat-dose oral toxicity studies (Office of Water Chemicals; Final Test Rule, 1993: 59,667). This testing was coordinated between API and the chemical manufacturer of 1,3,5-TMB. The results were provided to EPA for review (TSCA Chemical Testing; Receipt of Test Data, 1995; 32,320) and later published (Adenuga et al., 2014).

3.2. EPA's High Production Volume (HPV) Challenge Program

In cooperation with the U.S. EPA, the chemical and petroleum industries undertook the High Production Volume (HPV) Challenge, a voluntary program to assess the hazards of substances manufactured at a million pounds or more annually (USEPA, 1998). The HPV Challenge involved preparing a summary of existing information and the development of new information, such as toxicity testing, needed to fulfill the endpoints specified in the Organization for Economic Co-operation and Development (OECD) Screening Information Data Set (SIDS) program (USEPA, 2013).

The petroleum industry is one of the leading contributors to the Challenge Program. Through the Petroleum HPV Testing Group (Testing Group), the industry sponsored submissions on approximately 400 petroleum HPV substances – a commitment that covered almost 20% of the total number (approximately 2200) of HPV substances needing sponsorship (USEPA, 1998). These submissions, mostly covering intermediate products and blending streams, are grouped into product categories in order to best organize, summarize, and present the information in the context of downstream petroleum products (e.g., gasoline, jet fuel, and diesel fuel).

For the Gasoline Blending Streams Category, the Testing Group reviewed and assessed potential environmental and human health hazards from 81 refinery streams (e.g., naphthas) that could be used in the blending of gasoline. The test plan for this category considered the compositional range (paraffins, olefins, naphthenes, and aromatics – PONA) of various gasoline blending streams and assessed how variations in those constituents might impact the hazards/toxicity of the stream. API's test plan was well received by public commenters who found that the studies on the four PONA classes "contain as much or more of a given chemical class as is found in gasoline" (USEPA, 2014c). Two new studies were recommended on substances in the Gasoline Blending Streams category because of the richness of the existing data set. Specifically, these studies were conducted using OECD Test Guideline 422, combined repeat dose toxicity with reproductive/developmental toxicity, (OECD, 1996) and OECD Test Guideline 301F, ready biodegradability (manometric respirometry), (OECD, 1992) on a sample of highly naphthenic (cycloparaffins) naphtha, CAS registry number 64741-41-9 (McKee et al., 2014; Swigert et al., 2014).

The final category assessment document, including all additional testing and reviews, was completed and submitted to EPA in 2008 and is available at: Gasoline Blending Streams Category (USEPA, 2014d) or the API-managed website (API, 2014a). In addition, the robust summaries of these data are available on the API toxicology database for petroleum substances; see: http://www.apitox.api.org/ (API, 2014c). The Category Assessment Document submitted to EPA concludes that: "Results from studies on gasoline blending streams demonstrate that these naphthas have similar low toxicity profiles for human health endpoints. Ecotoxicity results generally fall within the moderate toxicity range. Results from tests of formulated gasoline are consistent with results from these streams, thus supporting the conclusion that there is no

distinction by hydrocarbon PONA class in the majority of the hazard endpoints evaluated. Therefore, the range of values from those studies can be used to characterize the untested substances in this category. In addition, exposure to these gasoline blending naphthas is minimal since they are typically production site limited, and thus are unlikely to pose a significant hazard to the environment or human health."

In its Screening-Level Hazard Characterization for the Gasoline Blending Streams Category (USEPA, 2011), EPA concluded that no data gaps were identified under the HPV Challenge Program.

3.3. EPA's Voluntary Children's Chemical Evaluation Program

Under the Voluntary Children's Chemical Evaluation Program (VCCEP), EPA under took a pilot program to seek industry sponsors to assess approximately 20 chemicals regarding specific toxicity endpoints, exposure, and risk. Among the chemicals were the individual gasoline constituents benzene, toluene, ethylbenzene, and three xylene isomers. The final output of this program was an assessment document that underwent independent peer-review. Both the assessment document and the peer-review findings were evaluated by EPA (USEPA, 2014e).

3.4. Methyl Tertiary-Butyl Ether Water Quality Criteria Work Group

A public/private partnership was established in 1997, under the administrative oversight of API, to develop aquatic toxicity data sufficient to calculate ambient water quality criteria for methyl tertiary-butyl ether (MTBE), a gasoline oxygenate. The MTBE Water Quality Criteria Work Group consisted of representatives from private companies, trade associations, and the U.S. EPA. The results were published (Mancini et al., 2002; Rausina et al., 2002) and used by EPA for surface water quality management purposes.

4. Product Stewardship Programs

The petroleum industry regularly conducts assessments of its products, process streams, constituents, and operations, etc. Specifically, the American Petroleum Institute (API) and others have conducted numerous toxicology studies and industry participates in product stewardship initiatives, such as those undertaken by CONCAWE (Conservation of Clean Air and Water Europe), the Petroleum Product Stewardship Council (PPSC), and Total Petroleum Hydrocarbon Criteria Working Group (TPHCWG). These initiatives provide hazard characterization data and establish a common set of risk benchmarks for addressing petroleum exposure from contaminated sites.

4.1. American Petroleum Institute

The American Petroleum Institute (API) was established in 1919 and has conducted hundreds of toxicology studies to evaluate the potential hazards and risks of petroleum substances. Most of the research has been cataloged and is available through API's Publications group at API (2014b) and IHS (2014). API has conducted numerous studies on acute toxicity, chronic toxicity, cancer, reproductive and development toxicity, genotoxicity, immunotoxicity, irritation, absorption, and other health aspects of gasoline, gasoline streams (e.g., naphthas), and chemical constituents of gasoline (e.g., hexane). API has also conducted environmental fate and effects studies on many of these same petroleum products and streams. Gasoline exposure assessment studies at service stations have also been done (Clayton, 1993; NATLSCO, 1995).

Table 2
Summary of API sponsored toxicology studies on gasoline*.

Gasoline and refinery process streams	Constituents of gasoline
33 Studies on unleaded gasoline	23 Studies on n-hexane, hexane isomers and commercial hexane
30 Studies on catalytically reformed naphtha	22 Studies on benzene
12 Studies on light alkylate naphtha	21 Studies on toluene and toluene concentrate
42 Studies on catalytically cracked naphtha	8 Studied on xylene and mixed xylenes
12 Studies on sweetened naphtha	6 Studies on TAME
10 Studies on thermally cracked naphtha	6 Studies on MTBE
9 Studies on sweetened naphtha	

* See API (1995a) and/or API (1995b) for detail on the above studies.

As of 1995, API (as summarized in its January 1995 publication API, 1995a) had hundreds of toxicology studies for gasoline and related streams/constituents as shown in Table 2.

Summaries of these studies on gasoline and refinery process streams are available on API's internet toxicology database for petroleum substances; see http://www.apitox.api.org/ (API, 2014c).

4.2. CONCAWE (Conservation of Clean Air and Water Europe)

In 1964, the petroleum industry in Europe established CONCAWE (Conservation of Clean Air and Water Europe), a research organization to coordinate hazard characterization efforts on petroleum products and to study the impact of the industry on air and water quality. CONCAWE has sponsored a number of studies that provide valuable hazard characterization data on gasoline, especially in the aquatic toxicity area (CONCAWE, 1995a,b,c,d,e,f,g, 1996a,b,c). CONCAWE has also sponsored research on the reproductive toxicity of gasoline vapors (McKee et al., 2000) and quantified exposure to gasoline vapors to employees and consumers (CONCAWE, 1997, 2009).

4.3. Total Petroleum Hydrocarbon Criteria Working Group

In 1993, the Total Petroleum Hydrocarbon Criteria Working Group (TPHCWG) was formed as a voluntary initiative of industry and other stakeholders to develop a set of clear, scientifically-based, health benchmarks for use primarily during clean-up at sites with petroleum/hydrocarbon contamination. The Working Group was formed to address the use of diverging clean-up requirements by various federal, state, and local agencies. The Working Group was guided by a steering committee consisting of representatives from industry, government, and academia. Some of the active participants among the more than 400 groups involved included the Gas Research Institute, the Petroleum Environmental Research Forum, major petroleum companies, the American Petroleum Institute, the Association of American Railroads, several state governments (i.e., Washington, Texas, Colorado, Hawaii, Louisiana, New Mexico), EPA, and the U.S. Department of Defense.

The TPHCWG developed methods to divide petroleum fuels and products into hydrocarbon groups or fractions based on carbon number, chemistry, environmental fate and transport considerations. Once the fractions were defined, fraction-specific values for a variety of properties (e.g., physical–chemical, fate, hazards) were developed and evaluated in order to develop toxicity criteria

(e.g., Reference Doses) for each fraction. The output of the TPHCWG work is available in a series of published documents (TPH Working Group, 1997a,b; 1998a,b; 1999) and has been used by the Center for Disease Control's Agency for Toxic Substances and Disease Registry (ATSDR) in its Toxicological Profile for Total Petroleum Hydrocarbons (ATSDR, 1999).

4.4. Petroleum Product Stewardship Council

The Petroleum Product Stewardship Council (PPSC) was incorporated in Washington, DC in 1994 with a goal of generating hazard information on refinery process streams used to blend transportation fuels. The original company members of PPSC were AMOCO, ARCO, BP, Chevron, Mobil, Texaco, and Unocal. PPSC's efforts were refocused on EPA's HPV Challenge Program (USEPA, 1998) when it began in 1999. The research sponsored by PPSC included the development of methods to generate test articles that simulate real-world inhalation exposure to gasoline-range hydrocarbons. Procedures to generate, store, ship, and then regenerate gasoline-range vapor condensates at the testing laboratory were established by the work sponsored by PPSC. Three refinery process streams used to blend gasoline were evaluated for repeat-dose, neurotoxicity, reproductive, developmental, and aquatic toxicity (ABC Laboratories, Inc., 1998a,b,c,d,e,f,g,h; Bui et al., 1998; Lapin et al., 2001; Schreiner et al., 1998, 1999; Schreiner et al., 2000a,b; Springborn Laboratories, Inc., 1999a,b,c,d,e,f,g,h,i; Stonybrook Laboratories, Inc., 1995a,b,c,d,e,f,g,h).

4.5. Individual Company Studies

Several companies have conducted hazard studies on gasoline blending streams and voluntarily published or made the laboratory reports available for use in industry programs like EPA's HPV Challenge Program. Studies relevant to gasoline toxicology include: ARCO (1994), Dalbey and Feuston (1996), Dalbey et al. (1996), UTBL, Inc. (1992a,b,c,d), and UTBL, Inc. (1994).

5. Conclusions

The health and environmental hazards of gasoline have been very well studied through a combination of both regulatory and voluntary programs. These toxicology testing programs have generated significant hazard characterization data on gasoline and gasoline evaporative emissions, on the refinery process streams used to blend gasoline, and on certain individual chemical constituents found in gasoline. Additionally, the extent of gasoline exposure to both workers and consumers has been studied over the past several decades. These hazard and exposure data in their totality provide an extremely robust data set for the purposes of gasoline risk assessment; consequently, gasoline is amongst the most well studied products in commerce and has been well characterized for risk assessment and regulatory purposes.

Conflict of interest

Swick reports that he is an employee of the American Petroleum Institute. Jaques reports receiving personal fees from the American Petroleum Institute during the development of the manuscript submitted for publication and also personal fees from the American Petroleum Institute for additional consulting services outside the submitted work. Estreicher and Walker report receiving professional fees from the American Petroleum Institute during the development of the manuscript submitted for publication and also professional fees from the American Petroleum Institute for additional legal representation outside the submitted work.

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Glossary

Acronym: Definition
1,2,4-TMB: 1,2,4-Trimethylbenzene
1,3,5-TMB: 1,3,5-Trimethylbenzene
API: American Petroleum Institute
CONCAWE: Conservation of Clean Air and Water Europe
CAA: Clean Air Act; 1990 reauthorized version
CAS/CAS number: Chemical Abstract Service registry number – unique chemical identification number assigned by the Chemical Abstract Service and used by EPA and others.
DIPE: Di-isopropyl ether
ECA: Enforceable consent agreement
EPA: Environmental Protection Agency; see also U.S. EPA
ET: Ethyltoluenes
ETBE: Ethyl tertiary-butyl ether
EtOH: Ethanol
HPV: High Production Volume – more than 1 million pounds per year of production.
MTBE: Methyl tertiary-butyl ether
OECD: Organization for Economic Co-operation and Development
PONA: Paraffins, olefins, naphthenes, and aromatics – key chemical constituents in gasoline blending streams.
PPSC: Petroleum Product Stewardship Council
SIDS: Screening Information Data Set – dossier of chemical hazard information used by OECD to assess chemicals.
TAME: Tertiary-amyl methyl ether
TBA: Tertiary-butyl alcohol
TPHCWG: Total Petroleum Hydrocarbon Criteria Working Group
USEPA: United States Environmental Protection Agency
UVCB: **U**nknown or **V**ariable compositions, **C**omplex reaction products and **B**iological – a class of chemical substances that includes most gasoline blending streams.
VCCEP: Voluntary Children's Chemical Evaluation Program – U.S. EPA voluntary program to evaluate the hazard, exposure, and risk of select chemicals to children.