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Assessing the mammalian toxicity of high-boiling petroleum substances under the rubric of the HPV program

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ABSTRACT

In 1998, the US EPA announced the HPV Challenge Program, a voluntary chemical data collection effort. The Petroleum HPV Testing Group (PHPVTG[1]) volunteered to provide data on approximately 110 high boiling petroleum substances (HBPS), i.e. substances with final boiling points ⩾approximately 650 °F (343 °C). These HBPS are substances of unknown and variable composition (UVCBs) that are composed of numerous individual constituents. Toxicity studies have shown that some HBPS can produce systemic (repeat-dose) and developmental effects, and some are mutagenic under *in vitro* conditions. The papers in this supplement show that these effects are related to the profiles of aromatic constituents in these substances. Further, it is shown that the effects on selected repeat-dose and developmental toxicity endpoints and mutagenic activity in bacterial assays can be predicted from compositional information using models based on the aromatic-ring class profile, "ARC profile" as defined by gas chromatographic separation of the DMSO-soluble fraction of the starting materials. This chromatographic method and the predictive models provide an efficient means of characterizing for screening purposes the potential for repeat-dose, developmental effects and bacterial mutagenicity of HBPS and can reduce the number of animal tests that would be required if these tests were conducted on all 110 HBPS.

1. Introduction

The purpose of this paper is to provide a background and perspective to the other papers in this supplement.

In 2000, the United States Environmental Protection Agency (US EPA), in partnership with industry and environmental groups, announced a voluntary chemical data collection effort called the High Production Volume Challenge Program (US EPA, 2000). The HPV Challenge Program aimed to develop and make publicly available screening level health and environmental effects information on chemicals manufactured in or imported into the United States in quantities greater than one million pounds per year, a.k.a. high production volume (HPV) chemicals. In the HPV Challenge Program, producers and importers of HPV chemicals voluntarily "sponsored" chemicals. HPV sponsors committed to developing data summaries of relevant existing information and to conduct testing to fill essential data gaps. Approximately 400 of the sponsored substances are petroleum substances. Of these, approximately 110 are HBPS, i.e. substances with final boiling points ⩾approximately 650 °F (343 °C). These HBPS include substances such as asphalts, aromatic extracts, crude oils, gas oils, heavy fuel oils, lubricating oil basestock, waxes and related materials, and residual hydrocarbon wastes (API, 2002, 2003–e, 2004, 2008, 2009, 2010, 2011a–e, 2012). It is these 110 HBPS that are the substances of direct interest in this supplement.

The screening-level health and environmental effects information provided by HPV sponsors consisted of data from a battery of tests adopted by the Organization for Economic Cooperation

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[1] The Petroleum HPV Testing Group (PHPVTG) is an unincorporated group of manufacturers affiliated by contractual obligation to fund a voluntary data disclosure and toxicity testing program on certain petroleum-related chemical substances in response to EPA's HPV Challenge Program. The American Petroleum Institute (API) manages the Group's activities.

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and Development (OECD) as the minimum required to screen HPV chemical substances for toxicity (OECD, 2012). This internationally agreed-upon test battery, known as the "Screening Information Data Set" (SIDS), includes the following endpoints:

- Physical/chemical properties – melting point, boiling point, vapor pressure, *n*-octanol/water partition coefficient, and water solubility.
- Environmental fate – photolysis, hydrolysis, transport/distribution, and biodegradation.
- Ecotoxicity – studies in fish, invertebrates, and algae.
- Mammalian toxicity – acute toxicity; repeat dose toxicity; developmental and reproductive toxicity; mutagenicity (gene mutation and chromosomal aberration/damage assays).

As conceived by the OECD, the SIDS battery of tests is not intended to completely characterize a substance, but rather is intended to provide sufficient data to (1) allow an initial screening assessment, and (2) identify substances in need of more in-depth testing and assessment (US EPA, 2000; OECD, 2012).

At the start of the HPV Challenge Program, sponsors of chemicals submitted to EPA (1) a set of robust study summaries that summarized representative existing studies/data for each sponsored substance and (2) test plans that either justified an assessment that available data fulfilled the SIDS data requirements or identified data gaps and provided a means for obtaining the needed information. Sponsors had several options to fill data gaps:

- to read across available data from similar chemicals to untested chemicals;
- to conduct testing using OECD or other standard guidelines; or
- to use accepted predictive models.

Accordingly, within the petroleum industry HPV program, read across of available data from substances considered "similar" was used to characterize untested substances. When judged necessary, the industry conducted toxicity tests, following established guidelines. Predictive models were also developed and applied to characterize the repeat-dose, developmental toxicity, and *in vitro* mutagenicity endpoints that are among the SIDS data requirements. The development of these models, and suggested uses are described in papers included in this supplement.

2. Early focus on carcinogenicity and mutagenicity

Historically, the characterization of the toxicity of HBPS has focused on the dermal carcinogenic hazards of these substances. The focus on carcinogenicity was triggered by results from epidemiological studies that indicated there was an excess of skin cancer among workers using unrefined lubricating oils (Leitch, 1924). After extensive animal studies, it was found that the constituents of concern with regard to the dermal carcinogenic potential of HBPS were polycyclic aromatic compounds (PAC) (Gilman and Vesselinovitch, 1955; Twort and Fulton, 1929; Twort and Lyth, 1939; Twort and Twort, 1930, 1931, 1933).

In the first half of the 20th century "cracking" processes were developed by which high molecular weight hydrocarbons were broken down either by heating (thermal cracking or coking) or in the presence of a catalyst (catalytic cracking) into lower molecular weight constituents that were more suitable for fuels blending. As refineries began adding cracking capacity after the Second World War, it was recognized that the products from these units included relatively high-boiling, more aromatic streams. This led to further studies to characterize the dermal carcinogenic hazards of these newer process streams and to also assess the effectiveness of refining processes in removal or conversion of the carcinogenic constituents to minimize the dermal carcinogenic risks to the extent possible (e.g., Dietz et al., 1952; Smith et al., 1950, 1951).

One outcome of this work was a series of publications that summarized work to investigate the relationship of physical/chemical properties of petroleum-derived materials and their dermal carcinogenic properties (King et al., 1984; Lewis et al., 1984) and to then assess the effectiveness of refining practices in reducing dermal carcinogenic potential (Halder et al., 1984; Kane et al., 1984). Another was the development of screening tools that could be used to determine whether certain types of petroleum products were likely to be dermal carcinogens (Mackerer et al., 2003; Roy et al., 1988a,b). One of these is the IP346 test that measures the weight of the DMSO-soluble fraction of lubricant base oils and related materials (IP, 1993). It was shown that oils in which the DMSO-soluble material comprises >3 wt% of the original material are potential dermal carcinogens (CONCAWE, 1994), and this relationship was adopted in the EU to separate refined lubricant base oils from unrefined oils and aromatic extracts for classification and labelling purposes (EU, 1994). As an alternative approach, the Ames *Salmonella* test was optimized to measure mutagenic potential in lubricant base oils and related materials (Blackburn et al., 1984, 1986). Based on a correlation between the mutagenic index (MI), a parameter calculated from the initial slope of the dose–response curve and dermal carcinogenic potential, it was proposed to consider any lubricant base oil with an MI > 1 as a potential dermal carcinogen. The optimized *Salmonella* test was established as a standard method for use in assessing the dermal carcinogenic potential of mineral oils used in lubricant formulation (ASTM, 1995). Concurrent with the development of these two assays was the development of a GC-FID assay measuring 3–7-ring PAC content in a DMSO extract of oil, expressed as a percentage of the oil.

3. Characterization of the toxicity of HBPS – existing studies

As previously discussed, the HPV program required a characterization of the acute, repeat-dose, developmental and reproductive toxicities and the mutagenic potential of each sponsored substance. Since the available data on a variety of HBPS provided sufficient evidence that they were not acutely toxic, the Petroleum High Production Volume Testing Group (PHPVTG) focused on the potential for non-cancer hazards associated with repeated exposure.

The first published study that systematically assessed the potential for HBPS to produce effects unrelated to cancer summarized the results of 13 repeated dose and 11 developmental toxicity studies of gas oils, heavy fuel oil components and distillate aromatic extracts (Feuston et al., 1994). It was reported that repeated dermal application of these substances produced systemic effects including increased liver weight, decreased thymus weight, and reductions in the levels of certain hematological parameters. In developmental toxicity studies, the principal findings were increased resorption frequency and decreased fetal weight. The authors hypothesized that the aromatic constituents of these substances were the causative factors, and this was supported by evidence that the Lowest Observed Effect Levels (LOELs) in these studies were correlated (Spearman rank correlation) with concentrations of PACs. Although this initial paper provided presumptive evidence that PACs were the constituents of HBPS that caused these effects, the results could not be used prospectively as a means of assessing the toxicity of other, untested substances.

To extend these observations, the current authors obtained copies of the laboratory reports for these and other related studies. As described elsewhere in this supplement (McKee et al., 2013; Murray et al., 2013a; Nicolich et al., 2013; Roth et al., 2013), a total