# Appendix 2: Commentary on Concordance/Lack of Concordance Between Endpoints Selected for Modeling and Information from Other Reviews of Toxicology of PAH

## 1. Sources of Information

Information was available from four sources on the toxicology of PAH and PAC-containing petroleum streams:

- Information published by Feuston et al (1994)
- Published reviews of toxicology of individual PAH
- Studies sponsored by American Petroleum Institute (API) on petroleum substances, and
- Company laboratory reports that have not been published in the open literature

Brief comments on the information from each source is given below.

### a) Information published by Feuston et al

Feuston et al examined the correlation between the weight percentage of various chemical classes of compounds in thirteen refinery streams and the magnitude of various effects produced in rats treated dermally with these substances in repeat-dose and developmental toxicity studies.
The authors concluded:

> "*In general, toxicity was correlated with concentrations of polycyclic aromatic compounds (PAC) composed of 3, 4, 5, 6, and/or 7 rings (decreased thymus weight, increased liver weight, aberrant hematology and serum chemistry, increased incidence of resorptions, decreased fetal body weight), PAC containing nonbasic nitrogen heteroatoms (increased mortality, decreased body weight, decreased thymus weight, increased liver weight, decreased hemoglobin content, hematocrit level, decreased fetal body weight), and/or PAC containing sulphur heteroatoms (decreased red blood cell and platelet counts, increased sorbitol dehydrogenase). A relationship between 2- ring PAC and skin irritation was demonstrated. Severity of effect was ranked against concentration of component class and statistical significance determined by the rank order correlation of Spearman. For the 13 streams tested, the presence and severity of systemic and developmental toxicity were dependent upon the levels of PAC and nonbasic nitrogen PAC.*
>
> *It is reasonable to assume that refinery streams rich in 3- to 7-ring PAC, S-PAC, and nonbasic N-PAC (e.g., carbazole derivatives) would be toxic, not only to the adult animal, but to the fetus as well."*

Because the observed relationship between PAC and effects was based on only two variables it is not possible to take advantage of the differential information from several PAC ring concentration measures at the same time. Furthermore, since the observed relationship was based on ranks it is difficult to use for predicting dose-response relationships in untested materials, nor can it be used to define points of departure. Also, the relationship with the raw (unranked or observed) data is not very strong.

### b) Published reviews of toxicology of individual PAH

There is a limited database available for comparison (SCF, 2002; ATSDR, 1995; IPCS, 1998; IRIS 2007; RAIS, 2007). The link between PAHs and dermal carcinogenesis has been known for many years. Consequently, most of the research on pure PAHs has been on their carcinogenic properties and not on systemic, repeat-dose toxicity. The limited number of

repeat-dose studies of pure PAHs most commonly used oral routes of administration, and/or were conducted in mice. The TG found references to only two dermal repeat-dose studies, and these were conducted in mice. Thus, there are no studies on pure PAHs that are equivalent in design to the studies utilized in the current project, i.e. no studies of similar duration, route of dosing, or species. Despite these differences, summaries of the animal studies on pure PAHs show that the effects most commonly reported are similar in nature to those identified in this project, i.e. increased liver weight, hematologic effects, and effects on lymphatic organs. A table summarizing these studies and their findings is shown in **Table A2-1.** below:

**Table A2-1. Summary of reports of effects of PAH**

| Compound | Route | Species | Duration | Effect | Reference[a] |
|---|---|---|---|---|---|
| Acenaphthene | Oral | Rat | 32 days | • peripheral blood changes<br>• liver weight; hepatocellular hypertrophy; increased serum cholesterol<br>• pulmonary effect | Knobloch et al., 1969 (Cited in 3,4) |
| Acenaphthene | Oral | Mouse | 90 days | • liver weight; hepatocellular hypertrophy<br>• increased serum cholesterol | EPA 1989 (cited in 1,2,4) |
| Acenaphthene | Inhal. | Rat | 5 months | • blood effects (no details)<br>• glandular tissues (no details) | Reshetyuk et al., 1970 (Cited in 3) |
| Anthracene | SC | Mouse | 40 wks | • adverse lymphoid effects; increases in reticulum cells, accumulation of iron, decreased lymphoid cells, and dilated lymph sinuses | Hoch-Ligeti, 1941 (Cited in 3) |
| Anthracene | Diet | Rat | 550 days | • no observed effects | Schmahl, 1955 (Cited in 3) |
| Anthracene | Oral | Rat | Not specified | • decrease in hemoglobin, reticulocytosis, leukopenia, and increase in residual blood nitrogen | Volkova, 1983 (Cited in 3) |
| Anthracene | IP | Human | 9 wks | • hematologic toxicity - myelosuppression, characterized by leukopenia and thrombocytopenia | Falkson et al., 1985 (Cited in 3) |
| Anthracene | IP | Mouse | 14 days | • no observed effects on immune response | White et al., 1985 (Cited in 3) |
| Anthracene | Oral | Mouse | 13 wks | • no observed effects | EPA, 1989 (cited in 1,2,3) |
| BaP | Oral | Mouse | 180 days | • hepatic effects<br>• hematological effects (e.g., aplastic anemia and pancytopenia resulting in hemorrhage)<br>• in a "nonresponsive" strain (those not highly responsive to producing increased levels of cytochrome P-450 mediated enzymes) | Robinson et al. 1975 (cited in 1,3) |
| BaP | IP | Mouse | 14 days | • immunosuppression - suppression of antibody response (more pronounced effects apparent in "nonresponsive" mice) | White et al., 1985 (Cited in 3) |

| Compound | Route | Species | Duration | Effect | Reference[a] |
|---|---|---|---|---|---|
| BaP | IP | Mouse | 14 days | • immunosuppression -depression of the T-cell-dependent antibody response (more pronounced effects apparent in "nonresponsive" mice). | Blanton et al., 1986 (Cited in 3) |
| BaP | IP | Mouse | 5 days | • reduced thymic cellularity, alteration of thymocyte differentiation<br>• reduced cellularity of the bone marrow | Holladay and Smith, 1995 (cited in 2) |
| BaP | Oral | Rat | 35 days | • immunotoxic effects - decreased thymus and lymph nodes wts, decreased absolute and relative B cell numbers in the spleen and decreased numbers of red and white blood cells<br>• decreased serum IgM and IgA levels | De Jong *et al.,* 1999 (cited in 2) |
| BaP | Oral | Rat | 90 days | • liver weight | Kroese et al. 2001 (cited in 2) |
| Benz[a]anthracene | SubQ | Mouse | 40 wks | • dilated lymph sinuses & decreased lymphoid cells<br>• lymph glands contained increased numbers of reticulum (stem) cells & accumulation of iron<br>• decreased spleen weights | Hoch-Ligeti, 1941, (Cited in 3) |
| Benz[a]anthracene | SubQ | Rats | Several wks | • extravascular red blood cells in lymph spaces & presence of large pigmented cells | Lasnitzki and Woodhouse 1944 (Cited in 3) |
| Benz[a]anthracene | IP | Mouse | 12 hr | • severe degeneration of the thymus<br>• reduced spleen & mesenteric lymph nodes weights<br>• degeneration of bone marrow cells<br>• retardation of thyroid gland development | Yasuhira, 1964 (Cited in 3) |
| Benz[a]anthracene | Oral | Rat | ? | • injury to the intestinal epithelium<br>• progressive anemia | Philips et al., 1973 (Cited in 3) |
| Benz[a]anthracene | ? | ? | ? | • progressive anemia as well as agranulocytosis | Robinson, et al., 1975 (Cited in 3) |
| Dibenz[a,h]anthracene | SubQ | Mouse | 40 wks | • lymphoid tissue changes<br>• decreased spleen weights<br>• liver and kidney lesions<br>• increased number of lymph gland stem cells | Hoch-Ligeti, 1941 (Cited in 3) |
| Dibenz[a,h]anthracene | SubQ | Rats | Several wks | • pathological changes in the lymphoid tissues - extravascular red blood cells in lymph spaces & presence of abnormally large pigmented cells | Lasnitzki and Woodhouse, 1944 (Cited in 3) |
| Dibenz[a,h]anthracene | SubQ | Mouse | 12 days | • serum antibody levels | Malmgren et al.,1952 (Cited in 3) |

| Compound | Route | Species | Duration | Effect | Reference[a] |
|---|---|---|---|---|---|
| Dibenz[a,h]anthracene | SubQ | Mouse | 14 days | • depressed immune responses<br>• reduced absolute thymus weight | White et al., 1985 (Cited in3) |
| Fluoranthene | Oral | Mouse | 13 wks | • liver weight, centrilobular pigmentation, increased SGPT values<br>• hematological effects including decreased packed cell volume and hemoglobin content;<br>• kidney toxicity | EPA 1988 (cited in 1,2,4) |
| Fluoranthene | ? | Rats | Subchron | • nephropathy<br>increased liver weights & enzyme levels | U.S. EPA, 1988 (Cited in 3) |
| Fluorene | Oral | Mouse | 13 wks | • liver weight, increased hemosiderin<br>• increased SGPT levels<br>• hematological effects including decreased packed cell volume and hemoglobin content/concentration, red blood cell count<br>• spleen weight, increased hemosiderin<br>• kidney pathology | EPA 1989 (cited in 1,2,3,4) |
| 1-Methylnaphthalene | Diet | Mouse | 81 wks | • pulmonary alveolar proteinosis | Murata et al. 1993 (cited in 4) |
| 2-Methylnaphthalene | Dermal | Mouse | 61 wks | • lipid pneumonia | Emi and Konishi 1985 (cited in 4) |
| 2-Methylnaphthalene | Diet | Mouse | 81-wks | • pulmonary alveolar proteinosis<br>• brain & kidney wts increased<br>• decreased differential counts of stab (young) & segmented (adult) neutrophils<br>• increased lymphocyte counts | Murata et al. 1997 (cited in 4) |
| 2-Methylnaphthalene | Diet | Mouse | 13 wks | • no observable effects | Murata et al. (1997) (cited in 4) |
| 2-Methylnaphthalene/1-Methylnaphthalene Mixture | Dermal | Mouse | 30 wks | • pulmonary alveolar proteinosis | Murata et al. 1992 (cited in 4) |
| Naphthalene | Dermal | Human (infant) | Unknown | • hemolytic anemia | Schafer, 1951 (Cited in 3) |
| Naphthalene | Oral | Rat | 600 days | • no observed effects | Schmahl 1955 (Cited in 3) |
| Naphthalene | Oral | Rat | 11 wks | • liver toxicity<br>• kidney toxicity | Kawai, 1979 (cited in 2) |
| Naphthalene | Oral | Rats | 13 wks | • increased mortality<br>• clinical signs of toxicity<br>• kidney lesions (focal cortical lymphocyte infiltration and tubular degeneration) | NTP, 1980 (Cited in 3,4) |

| Compound | Route | Species | Duration | Effect | Reference[a] |
|---|---|---|---|---|---|
| | | | | • lymphoid depletion of thymus<br>• signs of anemia | |
| Naphthalene | Oral | Mouse | 13 wks | • transient clinical signs of toxicity (lethargy, rough hair coats, decreased food consumption) | NTP, 1980 (Cited in 3) |
| Naphthalene | Oral | Rat | 13 wks | • body weight<br>• nephropathy | BCL, 1980 (cited in 2) |
| Naphthalene | Unknown | Rat | 10 days | • increased liver weights<br>• increased aniline hydroxylase and lipid peroxidase activity | Rao and Pandya 1981 (Cited in 3) |
| Naphthalene | Oral | Mouse | 90 days | • decreased spleen weights<br>• decreased hepatic hydrocarbon hydroxylase activity | Shopp et al., 1984 (Cited in 3,4) |
| Naphthalene | Oral | Mouse | 90 days | • no discernable effects | Shopp, et al. 1984 (cited in 2) |
| Naphthalene | Oral/Inhalation | Human | Acute | • most common effects - hemolytic anemia associated with decreased hemoglobin and hematocrit values, increased reticulocyte counts, presence of Heinz bodies, & increased serum bilirubin levels | ATSDR, 1990 (Cited in 3) |
| Naphthalene | Inhal. | Mouse | 103 wks | • Respiratory tract inflammatory and regenerative | NTP1992; (Cited 4) |
| Pyrene | Oral | Rats | 40 days | • enlarged fatty livers in rats | White and White, 1939 (Cited in 3,4) |
| Pyrene | Oral | Mouse | 13 wks | • kidney toxicity<br>• increased liver weights<br>• slight hematological changes (decreased RBC count, packed cell volume (PCV), and hemoglobin levels (HGB).) | EPA, 1989 (cited in 2,3,4) |
| | | | | | |

[a] "cited in" refers to which general review(s) the study was noted in:
1 = ATSDR, 1995
2 = SCF, 2002
3 = RAIS, 2007
4 = IRIS, 2007

**c) Studies Sponsored by American Petroleum Institute**

API has sponsored many studies on PAC-containing petroleum materials. Almost all of the studies sponsored by the API were 28-day dermal studies conducted in the rabbit. In these studies, after the repeated dermal application of petroleum substances, skin irritation was regularly observed in animals while systemic effects were rarely observed.
Studies also lacked detailed PAC compositional data on test samples – making them unsuitable for the current evaluation.

**d) Company laboratory reports that have not been published in the open literature**

The repeat-dose and developmental effects of repeated dermal exposure to petroleum substances has been summarized by API in robust summaries for each of the respective petroleum substance categories. The pattern of effects, when they occur, is broadly similar for each of the categories crude oils, gas oils, fuel oils and aromatic extracts. In the repeat-dose studies these effects normally consist of skin irritation which may range from non to severe, an increase in liver weight, decrease in thymus weight, decreases in red cell count, hemoglobin

concentration, hematocrit and platelet count. Serum chemistry changes are less consistent but mostly include an increase in blood urea nitrogen and cholesterol. The organ weight changes are not always accompanied by histopathological changes.

The developmental toxicity studies were of two types: prenatal studies in which the litters were delivered by caesarean section and post natal studies in which the dams were allowed to deliver their young. The principal effects observed in these studies were decreased pup growth and survival. Among the prenatal studies, the endpoints most commonly affected were those of fetal survival and weight gain. Among the postnatal studies, the endpoints most commonly affected were those of offspring growth and survival (to day 4 which was the scheduled termination of these studies). In both the prenatal and postnatal developmental toxicity studies that were evaluated, many of the petroleum substances demonstrated the potential to cause an increase in fetal resorptions and a decrease in litter size. In extreme cases, these effects manifested themselves as decreased female fertility due to the loss of the entire litter. However, the loss of the entire litter was not typically the most sensitive endpoint in the developmental toxicity studies of the petroleum substances. In a few developmental toxicity studies on crude oil, distillate aromatic extract and syntower bottoms in which the test material was administered orally to rats as a large single dose during gestation there was some evidence of an increase in malformations. While some of these test materials may have limited teratogenic potential under certain conditions, it is clear that the most sensitive endpoints of developmental toxicity for these materials are endpoints of fetal survival and growth, not malformations.

## 3. Concordance/lack of concordance Between Endpoints Selected for Modeling and Data from Other Reviews of Toxicology of PAH

### 3.1. Repeat-Dose Studies

The biological endpoints selected for modeling in the present work are generally consistent (not inconsistent) with primary toxicity changes observed with administration of individual PAHs. This consistency lends support to the biological plausibility of the models that were developed and to the hypothesis that PACs are responsible for the toxicity observed with the petroleum streams reviewed here.

## 3.2. Developmental Toxicity Studies

### Human Observations

Epidemiological studies by researchers at Columbia University have reported an association between exposure to PAH and various endpoints of developmental toxicity, including decreased fetal growth (Choi et al., 2006; Jedrychowski et al., 2003; Perera et al., 2005a, 2006b, 2006). However, these are environmental studies involving exposure to multiple PAHs, as well as many other chemicals and factors. For example, studies were conducted of women exposed to PAH from New York City air or from World Trade Center dust. It is not possible to evaluate the potential impact of individual PAH in these studies since subjects were exposed to multiple chemicals, including multiple PAH. Importantly, it is difficult to draw any conclusions about the effects of PAH on fetal development from these studies because it is difficult to identify and control for confounding factors. While these studies are valuable for hypothesis generation, they are inadequate for drawing definitive conclusions about whether PAH causes developmental effects in humans.

### Toxicological Studies

A developmental toxicity study was reported in which two PAHs were administered dermally to pregnant rats on gestation days 0-20 (Dutson et al., 1997). Pregnant rats were given dermal doses of 2.5, 25, or 250 mg/kg/day of carbazole or benzo[a]carbazole. Carbazole produced no signs of maternal toxicity or developmental toxicity at doses up to 250 mg/kg/day. In comparison, 250 mg/kg/day of benzo[a]carbazole produced maternal toxicity (i.e., decreased body weight gain and food consumption) and developmental toxicity. The developmental toxicity consisted of decreased number of total and live pups on the day of parturition and decreased pup body weight gain (postnatal day 0 and 4). The signs of maternal and developmental toxicity were consistent with those observed in the developmental toxicity studies evaluated by the TG.

With respect to benzo[a]pyrene, the Scientific Committee on Foods (SCF, 2002) stated that "[T]here is clear evidence for developmental toxicity of benzo[a]pyrene in mice from oral and intraperitoneal administration in the form of embryonic and fetal death, reduced fetal weight, and malformations." However, the scientific evidence to support this statement is somewhat limited. In an early study, female rats were given diets containing 0 or 0.1% benzo[a]pyrene prior to mating, during mating, and during pregnancy (Rigdon and Rennels, 1964). According to the study authors, benzo[a]pyrene did not appear to affect fertility; however, there was suggestive evidence that benzo[a]pyrene had a deleterious effect on the survival and growth of the fetal offspring. Importantly, this study had many weaknesses and deficiencies, including small group sizes (3-5 pregnant females per group), and no reliable conclusions can be drawn. However, although this study is limited, the results are consistent with those of the studies evaluated by the TG and are supportive of the endpoints selected for evaluation..

The SCF summary also stated that "[I]n the rat, subcutaneous administration of benzo[a]pyrene caused fetal deaths and reduced fetal weight … (SCF, 2002). This statement appears to be based on a study by Bui et al. (1986). According to the authors, subcutaneous administration of 50 mg/kg of benzo[a]pyrene at different stages of gestation "affected the reproductive performance of pregnant rats by significantly increasing the number of resorptions and fetal wastage, and by decreasing the fetal weight."

A dose-related decrease in fetal survival was reported among the offspring of pregnant rats exposed to benzo[a]pyrene by inhalation on gestation days 11-20 (Archibong et al., 2002). The pregnant rats were exposed to 0, 25, 75 and 100 micrograms per cubic meter of benzo[a]pyrene for four hours per day.

Although there are limited data and some inconsistencies, the results of the developmental studies of benzo[a]pyrene, carbazole, and benzo[a]carbazole seem reasonably consistent with those available for review by the TG. Thus, it does seem plausible that the signs of

developmental toxicity (i.e., decreased fetal survival and growth) associated with the PAC profile are, in fact, due to systemic doses of PAHs (and presumably also the sulfur and nitrogen PACs, which could not be assessed directly because no toxicological data on these substances was found). A quantitative comparison of results is unlikely to provide much additional information because, in addition to the small number of studies, those conducted on pure PAH most commonly used the oral, intraperitoneal, and subcutaneous routes of administration; only one dermal developmental toxicity study was found. In addition, most of these studies were conducted in mice, not rats.

### 3.3. Reproductive Toxicity (laboratory animals)

Mackenzie and Angevine (1981) reported infertility in mice exposed *in utero* to benzo[a]pyrene. The study authors reported that oral administration of benzo[a]pyrene at levels up to 160 mg/kg/day significantly reduced fertility, number of live litters, and offspring weight gain. The authors also reported testicular atrophy and atrophic seminiferous tubules in male offspring of treated dams, as well as reduced fertility among the offspring of treated dams.

Disruption of testicular steroidogenesis and epididymal function was reported in male rats exposed to benzo[a]pyrene by inhalation for 10 days (Inyang et al., 2003). Sperm progressive motility and plasma testosterone were significantly decreased compared to controls at exposure concentrations of 75 micrograms per cubic meter and greater.

Inhibition of ovulation was observed in mice given a single intraperitoneal injection of benzo[a]pyrene (Swartz and Mattison, 1985). An effect on the number of corpora lutea was most pronounced at one week after treatment at dose levels above 1 mg/kg. According to the authors, the study results indicate that acute exposure to benzo[a]pyrene may have a transient adverse effect on follicle growth, ovulation, or formation of corpora lutea. The effect on the number of corpora lutea was not reversible over the course of this experiment at doses of 100 mg/kg/day or greater.

In a more recent study in female mice, Kristenson et al. (1995) suggested that benzo[a]pyrene suppressed the development of primordial oocytes during fetal development. These investigators examined the effect of benzo[a]pyrene given alone and in combination with lead. Benzo[a]pyrene was administered to pregnant mice by gavage on gestation days 7-16. According to the authors, the offspring of these dams showed markedly reduced fertility with few ovarian follicles compared to controls when treated with benzo[a]pyrene alone or in combination with lead.

Borman et al. (2000) compared the ovotoxicity of three PAHs (BaP, DMBA, and 3-MC) doses in rats and mice given repeated intraperitoneal doses. All three PAHs produced ovotoxicity; however, DMBA was the most potent ovarian toxicant.

Others have reported that *in utero* exposure to pure PAH results in long lasting immune suppression in the offspring (Urso and Gengozian, 1982, 1984; Rodriguez et al. 1999).

The design of the developmental toxicity studies available to the TG did not assess testicular development, ovarian toxicity, or immune system effects, so a direct comparison based on these endpoints is not possible. However, there was little evidence of toxicity to reproductive organs observed in the repeat dose studies evaluated by the TG. Thus, while there is evidence that large doses of individual PAHs (e.g., benzo[a]pyrene) in pure form may affect male and female reproductive toxicity, it appears that reproductive toxicity is not a sensitive endpoint for the petroleum substances evaluated by the TG.

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