**EPA's Response to Major Interagency Comments on the Interagency Science Consultation Drafts of the IRIS Toxicological Review of Benzo[a]pyrene**

August 2013

**Purpose:** The Integrated Risk Information System (IRIS) assessment development process of May 2009 includes two steps (Steps 3 and 6) where the Executive Office of the President and other federal agencies can comment on draft assessments. The following information is in response to comments from interagency reviewers that were received over several rounds of Step 3 review (prior to public comment and external peer review) as discussed below.

**History of Interagency Science Consultation (Step 3 of the IRIS Process) for the draft IRIS Toxicological Review of Benzo[a]pyrene:**

**June 2011** –Under the May, 2009 IRIS process, the Interagency Science Consultation step for benzo[a]pyrene was initiated in June 2011 and comments were received from Agency for Toxic Substances and Disease Registry (ATSDR), Office of Management and Budget (OMB), National Aeronautics and Space Administration (NASA), National Institute for Occupational Safety and Health (NIOSH), Council on Environmental Quality (CEQ), and Department of Defense (DOD). The complete original comments are posted on the IRIS website (www.epa.gov/iris). Comments on this draft (June 2011) were taken into consideration in revising the June 2012 interagency science consultation draft. Revisions to the draft included increased discussion of the epidemiological data in support the weight of evidence descriptor; increased discussion of alternative modes of action for cancer; clarification regarding the selection of studies and endpoints for consideration in dose-response analysis and application of uncertainty factors. EPA responses to these comments are not discussed in detail here. In addition to considering previous interagency comments, the document was revised in response to the 2011 recommendations on IRIS assessments from the National Research Council (NRC, 2011).

**June 2012** – A revised interagency science consultation draft was provided to the Executive Offices of the President and other federal agencies for further comment in June 2012. Comments on this draft (June 2012) were received from ATSDR, NASA, NIOSH, CEQ, and DOD. The complete original comments are posted on the IRIS website (www.epa.gov/iris).

**August 2013**-The June 2011 and June 2012 interagency science consultation drafts of the Toxicological Review of Benzo[a]pyrene and external peer review charge questions, interagency comments on these draft documents, and EPA's Response to Major Interagency Comments on the Interagency Science Consultation Drafts are posted on the IRIS website (www.epa.gov/iris).

For a complete description of the IRIS process, including Interagency Science Consultation step, visit the IRIS website (www.epa.gov/iris).

**Selected Major Interagency Science Consultation Comments and Responses:**

**Topic #1: Inclusion of toxicogenomic data in the Toxicological Review of Benzo[a]pyrene-** *DOD noted that microarray data for benzo[a]pyrene is available but was not discussed in the benzo[a]pyrene assessment. DOD requested that a discussion be included as to why genomics data are not useful, even in a supporting role, at this stage.*

**EPA RESPONSE:** An analysis of the available microarray data for benzo[a]pyrene has been conducted and

added to the Supplemental Information to the Toxicological Review, and a summary of the findings has been added to the Toxicological Review.

**Topic #2: The development of reference values based on developmental studies -** *An overall RfD and an RfC were derived for benzo[a]pyrene using developmental endpoints for which the period of exposure involved developmental windows which are shorter than the duration considered to be a chronic exposure duration. DOD commented that this shorter exposure timeframe is not applicable in risk assessment of chronic exposures. DOD recommended EPA reconsider using developmental endpoints as candidate RfCs and RfDs and that these studies would be better suited for deriving specific developmental toxicity reference values.*

**EPA RESPONSE:** The database for benzo[a]pyrene was considered sufficient to allow for the calculation of organ/system-specific RfDs for reproductive toxicity, developmental toxicity, and immunotoxicity. The organ/system specific RfDs derived for reproductive and immunotoxic effects were both based on a chronic exposure inferred from subchronic exposure duration. The organ/system specific RfD based on neurodevelopmental effects was based on an exposure during the early postnatal period which is a heightened period of susceptibility for brain development. Of the organ/system-specific RfDs derived for benzo[a]pyrene, the RfD based on neurodevelopmental effects was the most sensitive and therefore was selected to serve as the proposed overall RfD to be protective of the general human population, including sensitive lifestages.

For inhalation exposure, the derivation of multiple organ/system-specific reference doses were considered for effects observed and identified as potential hazards of benzo[a]pyrene (developmental and reproductive toxicity). However, an organ/system-specific RfC to represent reproductive toxicity could not be derived due to a high level of uncertainty, thus the overall RfC was selected based on the hazard of developmental toxicity.

The overall RfD or RfC is derived to be protective of all types of effects for a given duration of exposure and is intended to protect the population as a whole including potentially susceptible subgroups (U.S. EPA, 2002). For example, elevated exposures during developmental lifestages could potentially lead to an appreciable risk, even if average levels over a longer exposure duration were less than or equal to the RfD or RfC. However, certain exposure scenarios may require particular attention to the risk assessment population of interest in order to determine whether a reference value based on toxicity following developmental exposure should be used. For example, the use of an RfD or RfC based on developmental effects may not be appropriate for a risk assessment in which the population of interest is post-reproductive age adults.

Additional text was added to the document to clarify the intent of the proposed overall RfD and RfC (see Section 2.1.5. and 2.2.5.). EPA has also included charge questions (question D4 and D9) which request comment on the selection of the overall RfD and RfC based on developmental endpoints.

**Topic #3: Adequacy of the inhalation database to derive a reference value for benzo[a]pyrene -** *DOD commented that the inhalation studies in animals available for benzo[a]pyrene do not meet the "minimum database criteria" described in EPA's 1994 Methods for Derivation of Inhalation Reference Concentrations (RfCs) and Application of Inhalation Dosimetry. These guidelines state that a low confidence RfC requires "a well conducted subchronic inhalation bioassay that evaluated a comprehensive array of endpoints, including an adequate evaluation of portal of entry (respiratory tract) effects, and the establishment of an unequivocal NOAEL and LOAEL." DOD stated that based on these guidelines, the inhalation developmental and reproductive studies available for benzo[a]pyrene are insufficient to develop an RfC as lung effects were not sufficiently monitored and the duration is too short. DOD further commented that only a single 4 week inhalation study observed effects in the lungs and that the available chronic inhalation cancer bioassay by did*

*not report a histological examination of the lung. Therefore, DOD recommended that an inhalation RfC not be developed.*

**EPA RESPONSE:** Both EPA's 1994 *Methods for Derivation of Inhalation Reference Concentrations (RfCs) and Application of Inhalation Dosimetry* and 2002 *A Review of the Reference Dose and Reference Concentration Processes* (referred to below as the RfD/RfC technical panel report) include discussions of minimum datasets for the derivation of an RfD and RfC. In contrast to the 1994 *Methods for Derivation of Inhalation Reference Concentrations (RfCs) and Application of Inhalation Dosimetry* described above, the 2002 RfD/RfC technical panel report describes a minimum dataset for RfD or RfC derivation as a database with no human data but dose-response toxicity data (specific to the route and duration being evaluated) with the assessment of endpoints other than mortality.

Although lung effects were not specifically monitored in the reproductive and developmental study used as the basis of the RfC (Archibong et al., 2002), the available body of evidence for benzo[a]pyrene indicates that it is not a respiratory irritant. A 4-week inhalation study in rats assessed lung inflammation and cytotoxicity through bronchoalveolar lavage and lung histolopathology at 1 day, 2 weeks, 2 months, 6 months, and 12 months after exposure. No lung or nasal injury was detected with benzo[a]pyrene average daily exposure levels 100 times greater than the point of departure used for the RfC.

Furthermore, the benzo[a]pyrene inhalation database includes human and animal data which informs potential hazards. The available data of humans exposed to benzo[a]pyrene through PAH mixtures (using biomarkers for benzo[a]pyrene) suggests that benzo[a]pyrene exposure may pose health hazards including infertility, miscarriage, and reduced birth weight (Wu et al., 2010; Neal et al., 2008; Tang et al., 2006; Perera et al., 2005b; Perera et al., 2005a) and cardiovascular effects (Friesen et al., 2010; Burstyn et al., 2005). The human studies of PAH exposure are not currently sufficient to develop a non-cancer toxicity value for the inhalation route. However, several inhalation studies using benzo[a]pyrene alone are available in animals including several reproductive (not multi-generational) and developmental studies (Archibong et al., 2008; Ramesh et al., 2008; Wormley et al., 2004; Archibong et al., 2002)(Inyang et al., 2003; Wu et al., 2003), including one subchronic study (Ramesh et al., 2008).

The available studies of benzo[a]pyrene exposure in animals were considered sufficient to derive reference values. While no human data are available following exposure to benzo[a]pyrene alone, toxicity information including dose-response data applicable to the duration in question with assessment of endpoints other than mortality are available by the inhalation route. However, recognizing the importance of characterizing the strengths and limitations of the database, EPA has added text to describe more fully the extent of the database for inhalation routes (see Section 2.1.1. and 2.2.1.). In addition, EPA has applied a database uncertainty factor of 10 and has revised the draft to characterize the confidence in the RfC as low. EPA has included a charge question (question D6) to address the selection of studies and relevant endpoints for the derivation of candidate values for the RfC.

**Topic # 4: Selection of studies and application of uncertainty factors associated with the derivation of the RfD and RfC for benzo[a]pyrene -** *CEQ commented that the most appropriate studies and endpoints appear to have been selected for the derivation of the reference values. NASA commented that although benzo[a]pyrene has an extensive body of literature, EPA's choice of studies and application of composite uncertainty factors of 300 and 3000 for the derivation of oral and inhalation reference values, respectively, raises questions as to the appropriateness of the chosen studies as the basis of these values. DOD commented specifically on the database uncertainty factor of 10 for the RfC and stated that is an over application of the uncertainty factor.*

**EPA RESPONSE:** The neurodevelopmental study by Chen et al. (2012) was selected as the basis of the overall RfD. It was a well-designed and well-conducted study that evaluated multiple neurobehavioral endpoints and measures of neurotoxicity in adolescent and adult rats. The candidate value from this study was selected as the overall RfD because the observed neurobehavioral changes represent a sensitive effect of benzo[a]pyrene exposure, with similar effects replicated across other studies (Bouayed et al., 2009; Grova et al., 2008). In addition, the neurodevelopmental study by Chen et al. (2012) is associated with the application of the smaller composite UF (300) compared to the organ/system-specific RfDs representative of immunotoxicity and reproductive toxicity.

The study by Archibong et al. (2002) was selected as the study used for the derivation of the overall RfC, as it was a well-designed and well-conducted study that observed biologically significant effects at the lowest dose tested by the inhalation route. This study indicates that the developing fetus is a sensitive target following inhalation exposure to benzo[a]pyrene and the observed decrease in fetal survival is the most sensitive noncancer effects observed following inhalation exposure to benzo[a]pyrene. Additional support for this endpoint is provided by a developmental/reproductive study conducted via the oral route (Mackenzie and Angevine, 1981) and by a human study which associated benzo[a]pyrene exposure with miscarriage (Wu et al., 2010). While the composite UF for the RfC of 3000 represents four areas of uncertainty, the database identifies developmental toxicity as a hazard following BaP exposure.

Text in Sections 2.1 and 2.2 has been expanded to further describe the oral and inhalation databases available for benzo[a]pyrene. Text was also added to further clarify the deficiencies in the benzo[a]pyrene databases. Additional discussion was also added describing the uncertainty factors applied to help extrapolate from a point of departure derived from less than chronic studies in laboratory animals to a lifetime human exposure at which effects are not anticipated to occur. Charge questions have been included (questions D3 and 8) requesting comment on the selection of the uncertainty factors in the derivation of candidate values.

**Topic #5: Use of toxicokinetic data to support a comparison between the RfD and RfC -** *DOD commented that a direct mathematical comparison of the RfD and the RfC yields a 350-fold difference in dose. DOD recommended that this difference be explicitly addressed in the document and that toxicokinetic information to support or refute this difference should be discussed.*

**EPA RESPONSE:** Additional information was added to the document to help describe what is known about quantitative differences in route specific toxicokinetics (see the Supplemental Information to the Toxicological Review). In the case of benzo[a]pyrene, absorption by the oral route is estimated to be approximately 10-30%, whereas absorption by the inhalation route is likely >80% (see the Supplemental Information to the Toxicological Review). First pass effects in the digestive tract, the liver, and the respiratory tract are also expected, due to differential expression and activity of enzymes responsible for the bioactiviation and neutralization of benzo[a]pyrene, which can greatly modify the systemically available dose.

Simple route-to-route extrapolation, as presented by DOD, where an inhalation concentration is converted to an oral dose (assuming an inhalation rate of 20 $m^3$/day) is not preferable because differences in toxicokinetics between exposure routes are not accounted for in this type of conversion (U.S. EPA, 2009, 2005, 2002, 1994). This method relies on the implicit assumption that the route of administration is irrelevant to the dose delivered to a target organ, an assumption considered quite uncertain and not supported by the principles of dosimetry or toxicokinetics (U.S. EPA, 1994). The preferred method for performing route-to-route extrapolation involves a validated pharmacokinetic model that describes the disposition of the chemical for the routes of interest (U.S. EPA, 1994). Several pharmacokinetic models of

benzo[a]pyrene have been developed for rodents, however, the models do not allow for cross-route extrapolation because models are not available which simulate the typical inhalation exposure to benzo[a]pyrene on poorly soluble carbonaceous particles (see the Supplemental Information to the Toxicological Review).

**Topic #6: Human relevance of benzo[a]pyrene-induced forestomach lesions and tumors -** *DOD recommended the inclusion of a discussion about the human relevance of forestomach effects and tumors observed in rodents following oral and inhalation exposure to benzo[a]pyrene given that humans do not have a forestomach.*

**EPA RESPONSE**: In addition to systemic tumors (liver, kidney, auditory canal, and mammary gland), forestomach tumors have been observed in rats, mice, and hamsters following dietary, gavage, and inhalation exposure to benzo[a]pyrene. The available data supports a mutagenic mode of action (MOA) for induction of these tumors, and key events of this MOA have been observed in the forestomach of rodents. In addition, benzo[a]pyrene-DNA adducts have been detected in oral and esophageal tissue obtained from smokers (Phillips, 2002) and several epidemiological studies have identified increased exposure to PAHs as an independent risk factor for esophageal squamous cell carcinoma (Abedi-Ardekani et al., 2010; Szymańska et al., 2010; Gustavsson et al., 1998). While humans do not have a forestomach, they do possess similar squamous epithelial tissue in their oral cavity (Wester and Kroes, 1988).

Additional text was added to the Toxicological Review to clarify that humans do not have a forestomach but that, for the above reasons, the forestomach tumors observed in rodents following benzo[a]pyrene exposure are supportive of a human hazard of carcinogenicity. In addition, EPA has included charge questions requesting comment on the selection of studies and relevant endpoints for dose-response analysis (questions D11 and 14).

**Topic #7: Consideration of additional modes of action (MOAs), including cytotoxicity and promotion, other than mutagenicity for benzo[a]pyrene carcinogenicity -** *DOD commented that the benzo[a]pyrene dose-response data for adducts and tumors in animal appear to suggest additional nonlinear MOAs may be operational. DOD suggested additional cancer MOAs be considered in the document.*

**EPA RESPONSE:** Animal bioassays are not, generally, designed to establish whether tumor responses have thresholds; they have insufficient power to detect increases as large as 1 in 100. In addition, nonlinear curves within the range of observation do not mean there is no risk at low exposures. Bioassay data cannot indicate how many MOAs there are, but rather can provide a basis for evaluating consistency with possible MOAs.

Cytotoxicity and mutation are not mutually exclusive modes of action; some observed effects can be consistent with more than one mode of action. A mutagen at high doses can cause cytotoxicity and regenerative proliferation that is a secondary response to massive DNA damage. Benzo[a]pyrene is a complete carcinogen; the contributing roles of other processes involved in the promotion and progression of benzo[a]pyrene-induced tumors, including cytotoxicity, inflammation, and regenerative cell proliferation, are acknowledged within the MOA discussion. The text was also expanded to discuss other potential contributors to benzo[a]pyrene-induced carcinogenicity, such as immune suppression, inflammatory responses, and AhR binding (i.e. regulation of benzo[a]pyrene metabolism/upregulation of progression related genes). However, there is not sufficient evidence that these mechanisms act independently of DNA damage and mutation to produce benzo[a]pyrene-induced tumors. A discussion to this effect was added to the cancer MOA section. In addition, EPA has included a charge question asking for comment on the conclusion that a mutagenic mode of action is the primary mode of action of benzo[a]pyrene-induced carcinogenicity (question C4).

**Topic #8: Consideration of data on biotransformation enzyme activity in infants and children and the application of age-dependent adjustment factors (ADAFs) -** *DOD commented that due to the decreased expression of bioactivation enzymes in early lifestages, children may be less susceptible to benzo[a]pyrene-induced carcinogenesis. DOD suggested that EPA include comparative data for age-specific metabolic activity. In addition DOD requested that EPA provide a stronger rationale for EPA's assertion that children are expected to be more susceptible to benzo[a]pyrene-induced carcinogenicity.*

**EPA RESPONSE:** EPA acknowledges that infants are generally understood to have lower expression of cytochrome p450 (CYP) enzymes (Ginsberg et al., 2004; Cresteil, 1998). Data in young animals indicate that benzo[a]pyrene exposure shortly after birth results in induction CYP1A1 (Wu et al., 2003) and increased carcinogenicity (Melikian et al., 1989; Vesselinovitch et al., 1975). However, studies in humans which quantitatively inform early postnatal expression of CYP1A1, the primary phase I bioactivation enzyme for benzo[a]pyrene, were not identified. While the degree of benzo[a]pyrene metabolism in the infant is unclear, numerous studies have indicated that this metabolism occurs in the developing fetus and in children, as indicated by the detection of benzo[a]pyrene specific DNA adducts, protein adducts, or urinary metabolites (Naufal et al., 2010; Ruchirawat et al., 2010; Suter et al., 2010; Mielzyńska et al., 2006; Perera et al., 2005a; Tang et al., 1999; Whyatt et al., 1998). Other toxicokinetic differences in infants and children may increase susceptibility to benzo[a]pyrene-induced carcinogenicity, such as decreased activity of Phase II detoxifying enzymes, increased liver to body mass ratio, and increased blood flow to the liver (Ginsberg et al., 2004; Pacifici et al., 1988).

An expanded discussion of age-related toxicokinetics of benzo[a]pyrene was added to the *Populations or Lifestages Particularly Susceptible to the Hypothesized Mode of Action* section of the Toxicological Review and the *Toxicokinetics* section (see the Supplemental Information to the Toxicological Review).

## REFERENCES


Abedi-Ardekani, B; Kamangar, F; Hewitt, SM; Hainaut, P; Sotoudeh, M; Abnet, CC; Taylor, PR; Boffetta, P; Malekzadeh, R; Dawsey, SM. (2010). Polycyclic aromatic hydrocarbon exposure in oesophageal tissue and risk of oesophageal squamous cell carcinoma in north-eastern Iran. Gut 59: 1178-1183. http://dx.doi.org/10.1136/gut.2010.210609

Archibong, AE; Inyang, F; Ramesh, A; Greenwood, M; Nayyar, T; Kopsombut, P; Hood, DB; Nyanda, AM. (2002). Alteration of pregnancy related hormones and fetal survival in F-344 rats exposed by inhalation to benzo(a)pyrene. Reprod Toxicol 16: 801-808.

Archibong, AE; Ramesh, A; Niaz, MS; Brooks, CM; Roberson, SI; Lunstra, DD. (2008). Effects of benzo(a)pyrene on intra-testicular function in F-344 rats. Int J Environ Res Public Health 5: 32-40. http://dx.doi.org/10.3390/ijerph5010032

Bouayed, J; Desor, F; Rammal, H; Kiemer, AK; Tybl, E; Schroeder, H; Rychen, G; Soulimani, R. (2009). Effects of lactational exposure to benzo[alpha]pyrene (B[alpha]P) on postnatal neurodevelopment, neuronal receptor gene expression and behaviour in mice. Toxicology 259: 97-106. http://dx.doi.org/10.1016/j.tox.2009.02.010

Burstyn, I; Kromhout, H; Partanen, T; Svane, O; Langård, S; Ahrens, W; Kauppinen, T; Stücker, I; Shaham, J; Heederik, D; Ferro, G; Heikkilä, P; Hooiveld, M; Johansen, C; Randem, BG; Boffetta, P. (2005). Polycyclic aromatic hydrocarbons and fatal ischemic heart disease. Epidemiology 16: 744-750. http://dx.doi.org/10.1097/01.ede.0000181310.65043.2f

Chen, C; Tang, Y; Jiang, X; Qi, Y; Cheng, S; Qiu, C; Peng, B; Tu, B. (2012). Early postnatal benzo(a)pyrene exposure in Sprague-Dawley rats causes persistent neurobehavioral impairments that emerge postnatally and continue into adolescence and adulthood. Toxicol Sci 125: 248-261. http://dx.doi.org/10.1093/toxsci/kfr265

Cresteil, T. (1998). Onset of xenobiotic metabolism in children: Toxicological implications. Food Addit Contam 15: 45-51. http://dx.doi.org/10.1080/02652039809374614

Friesen, MC; Demers, PA; Spinelli, JJ; Eisen, EA; Lorenzi, MF; Le, ND. (2010). Chronic and acute effects of coal tar pitch exposure and cardiopulmonary mortality among aluminum smelter workers. Am J Epidemiol 172: 790-799. http://dx.doi.org/10.1093/aje/kwq208

Ginsberg, G; Hattis, D; Sonawane, B. (2004). Incorporating pharmacokinetic differences between children and adults in assessing children's risks to environmental toxicants [Review]. Toxicol Appl Pharmacol 198: 164-183. http://dx.doi.org/10.1016/j.taap.2003.10.010

Grova, N; Schroeder, H; Farinelle, S; Prodhomme, E; Valley, A; Muller, CP. (2008). Sub-acute administration of benzo[a]pyrene (B[a]P) reduces anxiety-related behaviour in adult mice and modulates regional expression of N-methyl-D-aspartate (NMDA) receptors genes in relevant brain regions. Chemosphere 73: S295-S302. http://dx.doi.org/10.1016/j.chemosphere.2007.12.037

Gustavsson, P; Jakobsson, R; Johansson, H; Lewin, F; Norell, S; Rutkvist, LE. (1998). Occupational exposures and squamous cell carcinoma of the oral cavity, pharynx, larynx, and oesophagus: A case-control study in Sweden. Occup Environ Med 55: 393-400.

Inyang, F; Ramesh, A; Kopsombut, P; Niaz, MS; Hood, DB; Nyanda, AM; Archibong, AE. (2003). Disruption of testicular steroidogenesis and epididymal function by inhaled benzo(a)pyrene. Reprod Toxicol 17: 527-537.

Mackenzie, KM; Angevine, DM. (1981). Infertility in mice exposed in utero to benzo(a)pyrene. Biol Reprod 24: 183-192.

Melikian, AA; Bagheri, K; Hecht, SS; Hoffmann, D. (1989). Metabolism of benzo[a]pyrene and 7 beta,8 alpha-dihydroxy-9 alpha, 10 alpha-epoxy-7,8,9,10-tetrahydrobenzo[a pyrene in lung and liver of newborn mice. Chem Biol Interact 69: 245-257.

Mielzyńska, D; Siwińska, E; Kapka, L; Szyfter, K; Knudsen, LE; Merlo, DF. (2006). The influence of environmental exposure to complex mixtures including PAHs and lead on genotoxic effects in children living in Upper Silesia, Poland. Mutagenesis 21: 295-304. http://dx.doi.org/10.1093/mutage/gel037

Naufal, Z; Zhiwen, L; Zhu, L; Zhou, GD; Mcdonald, T; He, LY; Mitchell, L; Ren, A; Zhu, H; Finnell, R; Donnelly, KC. (2010). Biomarkers of exposure to combustion by-products in a human population in Shanxi, China. J Expo Sci Environ Epidemiol 20: 310-319. http://dx.doi.org/10.1038/jes.2009.19

Neal, MS; Zhu, J; Foster, WG. (2008). Quantification of benzo[a]pyrene and other PAHs in the serum and follicular fluid of smokers versus non-smokers. Reprod Toxicol 25: 100-106. http://dx.doi.org/10.1016/j.reprotox.2007.10.012

NRC (National Research Council). (2011). Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde: The National Academies Press. http://www.nap.edu/openbook.php?record_id=13142

Pacifici, GM; Franchi, M; Colizzi, C; Giuliani, L; Rane, A. (1988). Glutathione S-transferase in humans: development and tissue distribution. Arch Toxicol 61: 265-269. http://dx.doi.org/10.1007/BF00364848

Perera, FP; Rauh, V; Whyatt, RM; Tang, D; Tsai, WY; Bernert, JT; Tu, YH; Andrews, H; Barr, DB; Camann, DE; Diaz, D; Dietrich, J; Reyes, A; Kinney, PL. (2005a). A summary of recent findings on birth outcomes and developmental effects of prenatal ETS, PAH, and pesticide exposures [Review]. Neurotoxicology 26: 573-587. http://dx.doi.org/10.1016/j.neuro.2004.07.007

Perera, FP; Tang, D; Rauh, V; Lester, K; Tsai, WY; Tu, YH; Weiss, L; Hoepner, L; King, J; Del Priore, G; Lederman, SA. (2005b). Relationships among polycyclic aromatic hydrocarbon-DNA adducts, proximity to the World Trade Center, and effects on fetal growth. Environ Health Perspect 113: 1062-1067.

Phillips, DH. (2002). Smoking-related DNA and protein adducts in human tissues [Review]. Carcinogenesis 23: 1979-2004.

Ramesh, A; Inyang, F; Lunstra, DD; Niaz, MS; Kopsombut, P; Jones, KM; Hood, DB; Hills, ER; Archibong, AE. (2008). Alteration of fertility endpoints in adult male F-344 rats by subchronic exposure to inhaled benzo(a)pyrene. Exp Toxicol Pathol 60: 269-280. http://dx.doi.org/10.1016/j.etp.2008.02.010

Ruchirawat, M; Navasumrit, P; Settachan, D. (2010). Exposure to benzene in various susceptible populations: co-exposures to 1,3-butadiene and PAHs and implications for carcinogenic risk. Chem Biol Interact 184: 67-76. http://dx.doi.org/10.1016/j.cbi.2009.12.026

Suter, M; Abramovici, A; Showalter, L; Hu, M; Shope, CD; Varner, M; Aagaard-Tillery, K. (2010). In utero tobacco exposure epigenetically modifies placental CYP1A1 expression. Metabolism 59: 1481-1490. http://dx.doi.org/10.1016/j.metabol.2010.01.013

Szymańska, K; Matos, E; Hung, RJ; Wünsch-Filho, V; Eluf-Neto, J; Menezes, A; Daudt, AW; Brennan, P; Boffetta, P. (2010). Drinking of maté and the risk of cancers of the upper aerodigestive tract in Latin America: a case-control study. Cancer Causes Control 21: 1799-1806. http://dx.doi.org/10.1007/s10552-010-9606-6

Tang, D; Li, TY; Liu, JJ; Chen, YH; Qu, L; Perera, F. (2006). PAH-DNA adducts in cord blood and fetal and child development in a Chinese cohort. Environ Health Perspect 114: 1297-1300. http://dx.doi.org/10.1289/ehp.8939

Tang, D; Warburton, D; Tannenbaum, SR; Skipper, P; Santella, RM; Cereijido, GS; Crawford, FG; Perera, FP. (1999). Molecular and genetic damage from environmental tobacco smoke in young children. Cancer Epidemiol Biomarkers Prev 8: 427-431.

U.S. EPA (U.S. Environmental Protection Agency). (1994). Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry [EPA Report]. (EPA/600/8-90/066F). Research Triangle Park, NC. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=71993

U.S. EPA (U.S. Environmental Protection Agency). (2002). A review of the reference dose and reference concentration processes [EPA Report]. (EPA/630/P-02/002F). Washington, DC. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=51717

U.S. EPA (U.S. Environmental Protection Agency). (2005). Guidelines for carcinogen risk assessment [EPA Report]. (EPA/630/P-03/001F). Washington, DC. http://www.epa.gov/cancerguidelines/

U.S. EPA (U.S. Environmental Protection Agency). (2009). Risk Assessment Guidance for Superfund Volume I: Human Health Evaluation Manual (Part F, Supplemental Guidance for Inhalation Risk Assessment): Final [EPA Report]. (EPA/540/R070/002). Washington, DC. http://www.epa.gov/oswer/riskassessment/ragsf/index.htm

Vesselinovitch, SD; Kyriazis, AP; Mihailovich, N; Rao, KV. (1975). Conditions modifying development of tumors in mice at various sites by benzo(a)pyrene. Cancer Res 35: 2948-2953.

Wester, PW; Kroes, R. (1988). Forestomach carcinogens: pathology and relevance to man [Review]. Toxicol Pathol 16: 165-171.

Whyatt, RM; Santella, RM; Jedrychowski, W; Garte, SJ; Bell, DA; Ottman, R; Gladek-Yarborough, A; Cosma, G; Young, TL; Cooper, TB; Randall, MC; Manchester, DK; Perera, FP. (1998). Relationship between ambient air pollution and DNA damage in Polish mothers and newborns. Environ Health Perspect 106: 821-826.

Wormley, DD; Chirwa, S; Nayyar, T; Wu, J; Johnson, S; Brown, LA; Harris, E; Hood, DB. (2004). Inhaled benzo(a)pyrene impairs long-term potentiation in the F1 generation rat dentate gyrus. Cell Mol Biol (Noisy-le-grand) 50: 715-721.

Wu, J; Hou, H; Ritz, B; Chen, Y. (2010). Exposure to polycyclic aromatic hydrocarbons and missed abortion in early pregnancy in a Chinese population. Sci Total Environ 408: 2312-2318. http://dx.doi.org/10.1016/j.scitotenv.2010.02.028

Wu, J; Ramesh, A; Nayyar, T; Hood, DB. (2003). Assessment of metabolites and AhR and CYP1A1 mRNA expression subsequent to prenatal exposure to inhaled benzo(a)pyrene. Int J Dev Neurosci 21: 333-346.