Part A – Peer Review of the Background Document on Aristolochic Acid-Related Exposures: (1) Aristolochic Acid and (2) Botanical Products Containing Aristolochic Acid

The Report on Carcinogens (RoC) expert panel for aristolochic acid-related exposures met at the Sheraton Chapel Hill Hotel, Chapel Hill, North Carolina on January 24-25, 2007, to peer review the draft background document on aristolochic acid-related exposures and make a recommendation for the listing status of (1) aristolochic acid and (2) botanical products containing aristolochic acid in the 12th Edition of the RoC. Members of the expert panel are as follows:

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One of the charges to this panel was to determine whether the information in the draft background document on aristolochic acid-related exposures is presented in a clear and objective manner, to identify any missing information from the body of knowledge presented in the document, and to determine the utility of the body of knowledge in the background document for drawing conclusions about the carcinogenicity of a candidate substance and for applying the RoC criteria for listing. Following the discussion of all sections of the draft background document the expert panel reached a consensus concerning the critique of the draft background document, including its adequacy and any proposed revisions and voted 6 yes/0 no to accept the draft background document (with the proposed changes suggested by

the expert panel). Therefore, the expert panel agreed that the background document is adequate for drawing conclusions about the carcinogenicity of aristolochic acid-related exposures and for applying the RoC listing criteria.

The expert panel proposed revisions for each section of the aristolochic acid-related exposures background document are appended.

General comments

Define carefully in the glossary the terms contaminant or adulterant, avoiding the use of "intent" and use the two words consistent with these meanings throughout the document.

Abbreviations

- Page xvi: MeOH – This abbreviation is used for methanol, whereas methoxyl groups in molecules are usually referred to or denoted as MeO or OMe.

Glossary

- Define "adulterant," as "being made impure by mixing in a foreign or inferior substance" per Webster's dictionary and remove all reference to "intent." Define "contaminant" as "a substance inappropriately present in the environment that might cause harmful effects." A third category consists of products like guan mu tong which are properly labeled and contain botanicals containing AA. NTP should review document and make sure that these concepts are used consistently throughout.

Section 1: Introduction

1. General Introduction
   - Suggest renaming the document to the plural ("Aristolochic Acids"). Then revise document for consistency; i.e., when chemical species information is not available, use the plural.
   - Change Section 1 title from "Introduction" to "Introduction and Chemistry."
   - Page 1, line 14 – Add *A. clematitis, A. indica and A. serpentaria* to list of *Aristolochia* species.
   - Page 1, line 16 – Add obstetrics (to facilitate childbirth) and wound healing to the herbal medicine uses cited here.
2. Section 1.1 Chemical identification
   - Page 2, line 15 – After "Aristolochic acid I," add, "(also called aristolochic acid A)." After "AA II," add, "(also called aristolochic acid B)."
   - Page 2, lines 15-16 – "However, aristolochic acid I and its demethoxylated derivative, aristolochic acid II, are the predominant compounds and the most widely studied; …" Delete "the predominant compounds and."
   - Page 2, line 20 – After the Kumar *et al.* 2003 reference, insert a new sentence: "AA I and II are the most common marker compounds used to evaluate the presence of the family of aristolochic acids in plant samples."
   - Page 2, line 21 – Aristolochic acids are found in plants of both the *Aristolochia* and *Asarum* genera of the family Aristolochiaceae. Replace "are found" with "have been detected."
   - Page 3, Table 1-1
     - MeO should be substituted for MeOH each place where it appears in the table and the footnotes.
     - For the entry for *A. contorta*, E (or aristolochic acid E) refers to the same molecule as 7-MeO-8-OH-AA; therefore, one of these terms should be deleted. Also, check the accuracy for 6-MeO-AA methyl ester.
     - AAII and and VIIa should also be included in the components entry for *A. contorta*.
     - For the *A. debilis* entry, 7-methyl-AA I should be confirmed, it could possibly be 7-methoxy-AA I.
     - For the *A. clematitis* (Europe) entry, *clematitis* contains AAI, II, III, IV, IIIa and IVa. These acids should be included because they are important components of the AA mixture of the plant and also because they were reported for the first time.
   - Page 4, Table 1-3– Additional synonyms for AAII are 3,4-methylenedioxy-10-nitrophenanthrene-1-carboxylic acid, 3,4-methylenedioxy-10-nitro-1-phenanthrenecarboxylic acid, 3,4-methylenedioxy-10-nitro-1-phenanthroic acid (not 6-nitrophenanthro…).
3. Section 1.4 Aristolochic acid analogues: Page 8, Table 1-6
   - The structure for AA V is not correct (it is currently identical to the structure for aristolochic acid IVa). Aristolochic acid V was first reported for *Aristolochia argentina*. Its formula is 6,7-dimethoxy-3,4-methylenedioxy-10-nitro-1-phenanthroic acid. It was erroneously denoted as structure 105 in Kumar's review.
   - AA V is the O-methyl derivative of AA Va, and its MW is 371.
   - After Aristolochic acid IVa add "(aristolochic acid D)" and after Aristolochic acid V delete "(aristolochic acid D)."
   - For aristolochic acid VII change $COOCH_3$ to COOH; its MW is 371.

- The aristolactams (in *Aristolochia* spp.) are much more abundant than dioxoaporphines and show by far greater diversity than the dioxoaporphines and aristolochic acids, consequently a row for aristolactams (inserted previous to that for the dioxoaporphines) should be included, indicating variable structures depending on R.

Section 2: Human Exposure

1. Section 2.1 Use
   - Page 11, line 19 – "…in the early 1960s, it was tested for antitumor effects in mice (Kupchan and Doskovitch 1962) and in clinical trials, but the trials were discontinued when aristolochic acid was shown to be clinically ineffective and nephrotoxic (Jackson *et al.* 1964, Pezzuto *et al.* 1988)." Delete "clinically ineffective and" at the end of this line.
   - Page 11, line 20 – Delete the Pezzuto *et al.* 1988 reference.
   - Page 12 – Add two additional reports of cases of aristolochic acid nephropathy – (1) de Jonge and Vanrenterghem 2008, (2) Grollman and Jelakovic 2007 – to the paragraph beginning, "Over 100 cases…"
   - Page 12, line 5 – Insert "Aristolochic acid nephropathy (AAN) became recognized as a worldwide disease and," before, "after additional reports were reported . . ."
   - Page 12, line 7 – "After additional cases of aristolochic acid–associated nephropathy and carcinoma were reported in the United States, Europe, and Asia, the FDA (2000, 2001a, 2001c) issued warnings to healthcare professionals, industry associations, and consumers regarding the safety of botanical products and dietary supplements containing aristolochic acid." Add a period after "Asia" and start a new sentence with "In the early 2000s the FDA . . ."
   - Page 12, line 13 – "Nevertheless, plants containing aristolochic acid continue to be used in traditional and folk medicines for a number of indications and are still commercially available on the Internet (Gold and Slone 2003a, 2003b)." Change "are still occasionally," to, "have subsequently been shown to be." Also, add Schaneberg and Khan 2004 [already cited in background document] and Appendix A to references.
   - Page 12 – Add at end of paragraph: "Aristolochic acid-containing products, including *Aristolochia* species and products for which substitutions of other plants appeared to have occurred have been reported on the Dutch market (Martena *et al.* 2007)."
   - After the above add a new paragraph: "As described above, aristolochic acids (AA) were mainly found from Aristolochiaceous plants, especially the genera of *Aristolochia* and *Asarum*. The fruits of *Aristolochia contorta* and *A. debilis* are traditionally used as Ma Dou Ling for the treatment of cough, hemorrhoids, and other conditions related with lung in Chinese medicine. While their roots were used as Qing Mu Xiang for distention and pain of the chest and abdomen, diarrhea, hypertension, and snakebite, etc., their stem with leaves were used as Tian Xian Teng for the treatment of stomach pain, hernia pain, pregnancy edema, and rheumatic, etc. But some other Aristolochiaceous plants, such as *Aristolochia manshuriensis* (Mu Tong Ma Dou Ling), *A. kaempferi* (Da Ye Ma Dou Ling, crude drug name: Zhu Sha Lian), *A. moupinensis* (Huai Tong Ma Dou Ling, crude drug name: Huai Tong) are used legally as *Akebia* (Mu Tong) or its complementary and alternative in different places of China, although *Akebia* is mainly used for the treatment of urethritis, amenorrhea, and galactostasis. Some Aristolochiaceous plants such as the roots of *A. fangchi* (Fang Ji Ma Dou Ling, crude drug name: Guang Fang Ji) and *A. heterophylla* (Yi Ye Ma Dou Ling, crude drug name: Han Zhong Fang Ji) are also used as source plants of Fang Ji, which was originally obtained from the Menispermaceous plant *Stephania tetrandra* used for the treatment of edema and hand-foot convulsion. The overlapping use of different plants as one crude drug or one plant used as different crude drugs increases the risk caused by inadvertent consumption of aristolochic acids."

2. Section 2.3.1 Analysis methods
   - Page 15, line 2 – Add “fluorescence detection” to the list of detection methods (after “laser-induced fluorescence (LIF) detection”) and add “(Chan *et al.* 2007)” to the end of the sentence after “publications.”
   - Page 15, line 19 – 2 *mg/*g (2 ppm or 5.9 x 10^{-9} mol/g) should be revised to read 2 μ*g/*g (2 ppm or 5.9 x 10^{-9} mol/g).
   - Page 15, line 24 – Change 11 laboratories to 10 laboratories [description of the number of laboratories that were part of the collaborative study by Sorenson and Sullivan 2007].
   - Page 15, line 28 – Add Sorenson and Sullivan 2007 to cited references.
3. Section 2.3.2 Biological indices of exposure
   - Page 17, line 5 – “Aristolochic acid–DNA (AA-DNA) adducts have been identified in renal tissues of patients with Chinese herb nephropathy (Arlt *et al.* 2001b, Arlt *et al.* 2001a, Cosyns 2003, Gillerot *et al.* 2001).” After “Chinese herb nephropathy,” add, “using ^{32}P-post-labeling analysis.”
   - The NTP should add a new sentence to describe the Grollman *et al.* (2007) [already cited in background document] mass spectroscopy method.
4. Section 2.4.3 Occurrence and concentrations in botanical products
   - Page 23, line 9 – Add a paragraph after MCA 2002. Add to the beginning of the new paragraph the following sentences: “Two herbal remedies prepared from *Aristolochia debilis* or *A. contorta*, known, respectively, as Tian-Xian-Teng and Ma-Dou-Ling, appear in the official 2005 Chinese pharmacopeia. The use of these two remedies in China has been extensively recorded for over 1000 years.” Continue the new paragraph with the remainder of the previous paragraph, beginning with “The complexity of herbal nomenclature systems used in traditional medicines. . .”
   - Page 23, line 22 –Replace current language, “A multiple-to-one category describes multiple plant parts from the same species serving as different herbs.” with the following: “A multiple-to-one category describes multiple herbs derived from different part of same species of plant.”
   - Page 25, line 3 – “Plant substitutions such as those described above can be detrimental…” Replace “be detrimental” with “cause serious disease or death.”
   - Page 30 – Delete footnote concerning the second case reported by Consumer Reports which is not currently reported in Section 3 because no publication in the peer-reviewed literature was found; this case has now been reported in the peer-reviewed literature.
   - Page 30, line 20 –Add a description of the 4 cases reported by the British equivalent of the FDA. [Also, add descriptions of any case reports that are identified in the literature until such time as the final background document is published.]
5. Section 2.5 Regulations and Guidelines
   - Page 31, line 17 – Replace “Manufacturers are not required to record…” with “Manufacturers are required to record adverse events and to report to the FDA serious adverse events reported to them about their products.”
   - Page 32, line 15 – Add to the paragraph language about new current good manufacturing practice (cGMP) regulations on dietary supplements and how that relates to plant species identification and testing.
6. Section 2.6 Summary
   - Page 32, line 24 – Replace first sentence [“*Aristolochia* and related plants have been used since ancient times in traditional medicines by the Chinese, Native Americans, and other cultures.”] with: “The risk of human exposure to aristolochic acid remains a global problem. Native *Aristolochia spp.* have been used as herbal remedies for millennia in

virtually every country throughout the world, including Europe, Asia, Africa, North and South America.”

Section 3: Human Cancer Studies

1. Introduction
   - Page 36, line 10 – delete the word “possible” in this statement (“possible relationship with aristolochic acid”).
2. Section 3.1.2 Worldwide cases of herbal medicine nephropathy or of AAN
   - Page 39, lines 18-24 – “The review of the worldwide case reports has suggested that AAN has two clinical variants. Change “clinical variants” to “clinical presentations” in this text.
   - Page 39, line 28-29 – “Fanconi syndrome is characterized by proximal tubular dysfunction and slowly progressive renal dysfunction, which often is reversible when herbal treatment is stopped (Lee *et al.* 2004).” Change to, “which was described by the authors as reversible when herbal treatment was stopped.” and add, “see Section 5 for a discussion of Pozdzik *et al.* 2007.” Then add the following bracketed comment: “[However, an acute, limited phase of intoxication does not mean that a chronic phase will ensue, recovery from which could be interpreted as true reversibility.”
3. Section 3.1.2, Table 3.1 (pages 41-45)
   - Add to this table the following: (1) the case reported by Grollman *et al.* (2007), (2) the large clinical study of AAN by Dr. Xiaomei Li (if published before the background document is finalized, manuscript in preparation), and (3) 4 cases reported by the British equivalent of the FDA. The panel also recommended that Table 3.1 should be updated until such time as the final background document is published.
4. Section 3.2.2 Prevalence studies in the Belgian cases with AAN (beginning on page 47)
   - Add the expert panel-calculated estimated risk ratio [RR = 22] for the study reported by Nortier *et al.* 2000, [already cited in the background document] which used SEER data as the reference population. The assumptions for calculating the risk ratio are as follows: (1) approximately 25 cases with urothelial cancer, (2) estimated group exposed to AA =1500, (3) estimated duration of exposure = 3 years, (4) cancer rate in exposed group = 550/100,000 per year, (5) estimated background cancer rate (SEER) = 25, and (6) estimated risk ratio = 550/25= 22. [NTP should contact Dr. Albert Lowenfels for further details.]
   - Page 50, line 4 – Add a description of a case series of renal transplanted patients from the Belgian center, who suffered from bladder carcinoma several years after cessation of any aristolochic acid exposure (Lemy *et al*. 2008).
5. Section 3.3 Urothelial cancer and consumption of Chinese herbs (page 57)
   - Rename this section “Urothelial cancer and consumption of aristolochic acids” since it now includes studies of exposure to all botanical plants containing aristolochic acid.
   - Add results from study by Chang *et al.* 2007. This report lists the relative hazard of exposure to Chinese herbs for the development of transitional-cell carcinoma (TCC) as 6.2 ($P < 0.01$).
   - Page 57 – From the Li *et al.* 2005 paper (translation obtained by NTP), add the expert panel’s calculated odds ratio (37) and confidence interval (11 to 216) as a bracketed comment.
   - Add a description of Li *et al.* 2008, which reports TCC development in patients requiring renal transplantation. An increased risk of TCC was observed in patients with a history of taking herbal remedies with aristolochic acid compared to unexposed patients. [RR (calculated by the expert panel) = 5.6.]

6. Section 3.4 Balkan endemic nephropathy (BEN) and associated urothelial cancer (beginning on page 57)
   - General Comments:
     - Expand this section by adding a brief review of the more than 2000 cases of endemic upper urothelial carcinoma (UUC) analyzed by Nikolic (2006), noting that exposure to AA in this setting was not quantified.
     - Refer to "putative OTA adducts" or "OTA-related adducts" as appropriate throughout the document instead of "OTA adducts."
     - Describe results from the case-control study on BEN (Hranjec *et al.* 2005). This study evaluated the frequency (for the categories of observed "always" plus "sometimes") of seeing *A. clematitis* in the fields 20 to 30 years ago. The authors reported that this observation was significantly more frequent in subjects with endemic nephropathy (78.2%) than in subjects with other renal disease (33.3%) or healthy controls of the endemic regions (38%).
     - Describe results reported by Grollman *et al.* (2007) paper with AA-DNA adducts (i.e., expand on the description in the draft background document). Grollman and co-workers detected AA adducts in tumor tissue of 3 patients with urothelial cancer.
     - Move the Stewart *et al.* 2003 paper (currently on page 63 of the background document) to this section of the report.
     - Describe the A:T—>T:A "fingerprint" mutations in the Grollman *et al.* (2007) paper (expand on the description in the draft background document). Grollman and co-workers detected A to T transversions in 78% of patients with UUC who had a *p53* mutation.
   - Page 58, line 10 – Delete statement that aristolochic acid was found in wheat flour, but retain the observation that weed seeds were mixed in wheat. Clarify per Ivic 1970 paper [already cited in draft background document].
   - Page 58, line 1 – BEN is a "household," not a "familial" disease. The latter designation suggests a strong genetic inheritance, which does not apply to BEN.
   - Page 58, line *27* – Delete the first sentence, "Consumption of *Aristolochia* is not the only risk factor associated with BEN, and it may be that there are multiple risk factors."
   - Page 59, lines 19-23 – Use the exact language from the FAO/WHO 2006 report (published in EFSA Journal 2006) for their conclusions and review the primary literature from their report on OTA."
   - At the end of this section [page 59, line 23], add the information from The Panel on Contaminants in the Food Chain of the European Food Safety Authority (EFSA) review of OTA-related adducts and genotoxicity in conjunction with the discussion of the controversial data published by Pfohl-Leszkowicz and her collaborators. [This information is currently stated on page135 in the draft background document in Section 5.3.4]
7. Section 3.5.1 Association between botanical products containing aristolochic acid and nephropathy
   - Page 61, line 29 –*"* …(1) exposure to aristolochic acid alone causes nephropathy in experimental animals." Add—as a "numbered" item,"intravenous administration of AA caused renal toxicity in humans (Jackson *et al.* 1964)" [reference already cited in background document].
8. Section 3.6 Summary (page 64)
   - Line 12, insert "upper" before the words "urothelial cancer"

- Discuss the preference for aristolochic-acid induced tumors to localize in the upper urothelial tract of humans. The background document should provide important context by referring throughout the text to the unusual anatomical location of transitional cell (urothelial) carcinomas (TCC) associated with AAN. In the herb-induced TCC reported in Belgium and other countries, and in BEN-associated TCC, 90% of all tumors are located in the renal pelvis and/or upper ureter. In fact, the few bladder tumors observed occasionally in AAN might arise via “seeding” from the above-mentioned classical tumors. UUC represents only 5% of all detected TCC and have been associated with exposure to certain chemicals (e.g., phenacetin and arsenic (Genega and Porter, 2002)).

Section 4: Studies of Cancer in Experimental Animals

1. Section 4.2.1 Rat: Acute exposure
   - Page 67, line 2 – Change “nearly normal” to “lesions resolved.”
2. Section 4.2.2 Rat: Subchronic to chronic exposures
   - Page 77 - A. *fructus* does not appear to be a valid species name. NTP should investigate and correct if necessary.

Section 5: Other Relevant Data

1. General comments
   - Define carefully in the glossary the terms contaminant or adulterant, avoiding the use of "intent" and use the two words consistent with these meanings throughout the document.
2. Section 5.1 Absorption, distribution, metabolism, and excretion
   - Page 85, line 24 – Change "*In vitro* metabolism studies suggest that aristolochic acid I is preferentially metabolized by an oxidative pathway" to "*In vitro* metabolism studies suggest that AA-I is metabolized by oxidative and reductive pathways", citing Shibutani *et al*. (2007).
3. Section 5.2.1 Renal toxicity in humans
   - Page 90, line 15 – Add references from BEN literature [Cosyns 2003].
   - Page 90, line 17 – Change "The etiology of BEN is currently unknown, but chronic dietary intoxication from bread made from wheat flour contaminated with seeds of *A. clematitis* has been implicated (Arlt *et al.* 2007, Grollman *et al.* 2007, Hranjec *et al.* 2005, Ivic 1970, Stiborová *et al.* 2007)." to "Chronic dietary intoxication from bread made by wheat flour contaminated with seeds of *A. clematitis* has been implicated in the etiology of BEN (Ivic, 1970 (Ref 84 in draft background document), Hranjec *et al.* 2005 (Ref 76 in draft background document), Grollman *et al.* 2007 (Ref 69 in draft background document)."
4. Section 5.2.2 Toxicity in experimental animals
   - Add a description of the extensive studies on aristolochic acid toxicity in horses cited below, which provided the first clue to similarities between AAN and BEN: (1) Martincevic M. Toxic action of *Aristolochia clematitis* on the kidney of horses, *Veterinarski Arhiv* 27: 51-19 (1957); (2) Dumic A. Poisoning of horses by birthwort (*Aristolochia clematitis L*.) Belgrade Serbia, 1954 pp. 3-35.
   - Include a discussion of the time course of phenotypic changes of the proximal tubular epithelial cells, especially proliferation and apoptosis, in the rat model of aristolochic acid nephropathy (Pozdzik *et al.* 2007).
   - Page 91, line 17 – Add Dong *et al.* (2006) [already cited in draft background document] and Shibutani *et al.* (2007) [already cited in draft background document] to the references cited for aristolochic acid toxicity in mice (Hu *et al.* 2004, Sato *et al.* 2004).
5. Section 5.2.3 Toxicity to kidney or urinary tract cells *in vitro*
   - Page 107, lines 12 and 13 – Revise sentence, "Aristolactam derivatives of aristolochic acids also form DNA adducts…" to "Although aristolactam derivatives of aristolochic acids also form DNA adducts (see Section 5.3.1, below) and cause mutations in *Salmonella* (see Section 5.3.2, below), most studies show aristolactams to be non-toxic to mammalian cells (Wen *et al.* 2006, Zhang *et al.* 2005) [both references already cited in draft background document]."
6. Section 5.3.1 DNA adduct formation
   - Page 109, lines 8 to 16 – Insert the following new sentences beginning at the end of line 11: "There is a contrast between the *in vitro* data and the data in experimental animals and humans. Aristolactam-DNA adducts may persist for many years *in vivo* (add reference)." Delete bracketed comment on lines 12 to 16. "[Although there are several differences between these studies, particularly in the specific cell type used and in the doses of aristolochic acid tested (10 and 20 μM for Lebeau *et al.* and up to 5 μM for

Pfohl-Leszkowicz *et al.*), the reason for the contrast in the final conclusion of persistence of AA-DNA adducts in one study compared with the conclusion that these adducts do not persist in the other is unclear.]

7. Section 5.3.1: DNA adduct formation, Studies in humans with AAN or BEN
   - Page 115, lines 11 to 12 – Delete the word "three" before "long term residents" and add "Three" before "Tumor tissues were analyzed for adducts. . ."
   - Page 115, line 13 – Change "10^{7}" to "10^{8}" [adducts per nucleotides].
   - Page115, line 15 – Clarify that the 60 renal tissues were formalin-fixed paraffin-embedded samples.
   - Page 115, line 16 – Change "patients with nephropathy," to, "patients reported to have nephropathy."
   - Page 115, line 22 – Insert a statement noting that these patients did not have supporting clinical/pathology data.
   - Page 115, line 23 – Insert "Interpretation of," at the beginning of the sentence beginning with, "The data on OTA-DNA. . ."
   - At the end of this section [page 115, line 24], add the information from The Panel on Contaminants in the Food Chain of the European Food Safety Authority (EFSA) review of OTA-related adducts and genotoxicity in conjunction with the discussion of the controversial data published by Pfohl-Leszkowicz and her collaborators. [This information is currently stated in the draft background document in Section 5.3.4]. After [line 24], "The data on OTA-DNA adduct formation is controversial (see Section 5.3.5, Mutational spectra in tumors from animals and humans)." add the following references: Mally *et al.* 2004, Gautier J-C *et al.* 2001, Turesky 2005 [in draft background document], Palma *et al.* 2007, Cavin *et al.* 2007. Then add the statement, "The C-C8-dGMP-OTA adduct used as a standard was synthesized by photo-irradiation."

8. Mutational spectra in tumors from animals or humans
   - Page 134, line 18 – Change "DNA was isolated from fresh tumor tissues" to "DNA was isolated from fresh tumor tissue from 6 patients and from formalin-fixed, paraffin-embedded tissues from 5 patients.
   - Page 134, line 22 – Add a sentence to emphasize the mutational spectra from the upper urothelial tumors. "The p53 mutational spectra from patients with upper urothelial cancers associated with BEN are similar to those reported in the 2006 edition of the IARC p53 mutational database. The frequency and predominance of A:T to T:A transversions are suggestive of a mutational signature for human exposure to AA."
   - Page 134, line 23: Change the first paragraph beginning with "Arlt *et al.* (2007) recently proposed that. . ." to "Arlt *et al.* (2007) reviewed the use of mutational spectra as a means for studying the etiology of BEN-associated cancer. They discussed the mechanism of AA-induced carcinogenesis and the available data evaluating OTA and cancer. They noted that, although unequivocal…."
   - Page 135, lines 7 to 13 – At the end of line 13, add the references stated in comment 6 [Mally *et al.* 2004, Gautier J-C *et al.* 2001], Turesky 2005 [in draft background document], Palma *et al.* 2007, Cavin *et al.* 2007]. [This text describes EFSA review of OTA-related adducts and genotoxicity and the discussion of the controversial data published by Pfohl-Leszkowicz and her collaborators.]
   - Page 135 – Add a new paragraph at the end as a comment: "[Ochratoxin A (OTA) has never been demonstrated to be nephrotoxic (or carcinogenic) for humans despite its ubiquitous presence in common foodstuffs. There is no evidence that OTA is a direct-acting human carcinogen or that this mycotoxin plays a significant role as the cause of

endemic nephropathy or upper urothelial cancer Grollman and Jelakovic 2007) (de Jonge and Vanrenterghem (2008).]

9. Section 5.4.3 Metabolic activation and toxic effects in humans
   - Page 144, lines 4-5 – "However, no mechanistic explanation for the unusual rapidity of the onset of urinary-tract carcinoma in humans following *Aristolochia* consumption has been found as yet, and there are no data concerning the cancer risk in individuals who have consumed *Aristolochia* without evidence of renal impairment." Delete "as yet, and there are no data concerning the cancer risk in individuals who have consumed *Aristolochia* without evidence of renal impairment."

10. Section 5.5 Summary
    - Page 149, Line 4 – Delete the following sentence: "There is as yet no mechanistic explanation for the unusual rapidity of the onset of urinary-tract carcinoma in humans following *Aristolochia* consumption, nor are there data concerning the cancer risk in individuals who have consumed *Aristolochia* without evidence of renal impairment."

Report Approved Redacted Date 4/16/08

Arthur P. Grollman, M.D. (Chair)

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3. Chang CH, Yang CM, Yang AH. 2007. Renal diagnosis of chronic hemodialysis patients with urinary tract transitional cell carcinoma in Taiwan. *Cancer* 109(8): 1487-92.
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5. Dumic A. 1954. *Poisoning of horses by birthwort (Aristolochia clematitis L.)*, Belgrade, Serbia: p. 3-35.
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