Biblio_Ochratoxin A_12_17_14

1. Khoury A, Atoui A. Ochratoxin A: A general overview and actual molecular status. Toxins 2010; 2: 461-493.

   This paper presents basic information about the chemical structure of ochratoxin A (OA) and its many metabolites. OA is a remarkably stable toxin: once found on foodstuffs it will stay without effective removal by cooking, steam, pressure or irradiation. Toxicity is reviewed, with evidence of immunosuppression reported. Carcinogenesis in mice is noted but not in humans. Fungi that produce OA are diverse with multiple foods and beverages contaminated (short list: grapes, juice, must, wine, coffee, cereals, salami, ham, rice, corn, millet, spices and cheese). 50% of human daily intake of OA is due to contamination of cereal grains. Limits of OA consumption have been reduced from 100 ng/kg body weight to 14 ng/kg bw/day to be considered safe, but coffee consumption that leads to 5 micrograms/kg bw are safe! OA compounds are easily identified by chromatography methods. ELISA is rapid but is well documented to not be specific; "cross-reactivity with related molecules can vary widely giving over-estimated values."

   OA is made via the polyketide synthesis pathway. Structures are well represented. Genes for this pathway are tightly regulated, respond to environmental factors and are arranged in clusters. The p450-H11 gene involved in OA production is nearly identical to the gene involved in aflatoxin production. The p450-B03 gene is essentially the same as one of the trichothecene biosynthesis genes, suggesting conservation of horizontal transfer of gene sequences from one species to another. "Regions of homology within mycotoxin biosynthetic genes from the different species can be used to develop primers to detect the presence of …aflatoxin producers, trichothecene producers, fumonisin producers and patulin." (**NB**: environmental factors that turn on mycotoxin production by one species will activate many.) Beta tubulin-1 gene sequences are important in OA (**NB**: see benomyl chapter in Surviving Mold). PCR is being widely used for detection of OA in foodstuffs.

2. Pardo E, Marin S, Ramos A, Sanchis V. Effect of water activity and temperature on mycelia growth and ochratoxin a production by isolates of Aspergillus ochraceus on irradiated green coffee beans. J Food Prot 2005; 68: 133-8.

Maximum mycelial growth seen at a(w) of 0.95-0.99 at 30 degrees C. None at a(w) of 0.80. Maximum concentration of OA was 17,000 ng/g of green coffee. (**NB**: these levels will give very high urine concentration of OA).

3. Brakhage A, Bruns S, Thywissen A, Zipfel P, Behnsen J. Interaction of phagocytes with filamentous fungi. Curr Opin Microbiol 2010; 13: 409-15.

   Conidia of Aspergillus are killed by various immune effector cells; hyphae are killed by neutrophils. Neutrophil extracellular traps contain and localize fungal components preventing systemic spread. Th (1) responses results in improved defenses against infection.

4. Botterel F, Gross K, Ibrahim-Granet O, Khoufache K, Escabasse V, Coste A, Cordonnier C, Escudier E, Bretagne S. Phagocytosis of Aspergillus fumigatus conidia by primary nasal epithelial cells in vitro. BMC Microbiol 2008; 8; 97. doi: 10.1186/1471-2180-8-97.

   Human nasal epithelial cells phagocytose fungal conidia, preventing germination of spores.

5. Khoufache K, Puel O, Loiseau N, Delaforge M, Rivollet D, Coste A, Cordonnier C, Escudier E, Botterel F, Bretagne S. Verruculogen associated with Aspergillus fumigatus hyphae and conidia modifies the electrophysiological properties of human nasal epithelial cells. BMC Microbiol 2007; 7: 5.

   Verruculogen is found in up to 67 Aspergillus fumigatus extracts. It modifies electrophysiologic properties of cells in vitro. (**NB**: Cells in mucus will be sheltered from these effects.)

6. Frisvad J, Rank C, Nielsen K, Larsen T. Metabolomics of Aspergillus fumigatus. Med Mycol 2009; SUPPL 1: S53-71.

   At least 226 active secondary metabolites are made by A. fumigatus that come from at least 13 different families that can be identified by HPLC. Sphingofungins may play a similar role as fumonisins but often OA is misidentified.

7. Creppy, E, Baudrimont I, Marie A. J Toxicol Sciences 1998; 23 Supplement II 165-172. How aspartame prevents the toxicity of ochratoxin A.

   Delivery of phenylalanine by Asp disrupts protein synthesis disruption caused by OA.

8. Duarte S, Pena A, Lino C. Human ochratoxin A biomarkers—from exposure to effect. Crit Rev Toxicol 2011; 41: 187-212.

   Biomarkers for OA exposure are not related to time course of exposure given their long half life in serum.

9. Fazekas B. Tar A, Zomborszky-Kovacs M. Ochratoxin a contamination of cereal grains and coffee in Hungary in the year 2001. Acta Vet Hung 2002; 50: 177-88.

OA ingested in coffee can approach 4.1 ng daily while OA ingested from cereals is 6.7 ng. Foods of animal origin contaminated with OA could present OA/OA metabolites to consumers of animals.

10. Coronel M, Marin S, Cano-Sancho G, Ramos A, Sanchis V. Exposure assessment to ochratoxin A in Catalonia (Spain) based on the consumption of cereals, nuts, coffee, wine and beer. Food Addit Contam Part A Chem Anal Control Expo Risk Assess 2012; 29 979-93.

    OA is present in many food stuffs but total consumption in Catalonia was less than 14 ng/kg bw/day.

11. Thuvander A, Paulsen J, Axberg K, Johansson N, Vidnes A, Enghardt-Barbieri H, Trygg K, Lund-Larsen K, Jahrl S, Widenfalk A, Bosnes V, Alexander J, Hult K, Olsen M. Levels of ochratoxin A in blood from Norwegian and Swedish blood donors and their possible correlation with food consumption. Food Chem Toxicol 2001; 39: 1145-51.

    Blood levels of OA were determined in 406 asymptomatic patients using HPLC. Mean level was 0.18 ng/ml. No correlation between diet and plasma OA levels (**NB**: OA has long half life). However, cereal grain products, wine, beer and pork as well as brown bread did correlate with OA levels.

12. Leong S, Hocking A, Pitt J, Kazi B, Emmett R, Scott E. Australian research on ochratoxigenic fungi and OA. Int J Food Microbiol 2006; 111 Suppl 1: S10-7.

    80% of OA is removed from grapes during wine making.

13. Mateo R, Medina A, Mateo E, Mateo F, Jimenez M. An overview of ochratoxin A in beer and wine. Int J Food Microbiol 2007; 119: 79-83.

    OA is found in over 50% of wines. Red, rose and whites have decreasing amounts of OA.

14. Di Giuseppe R, Bertuzzi T, Rossi F, Rastelli S, Mulazzi A, Capraro J, de Curtis A, lacoviello L, Pietri A. Plasma ochratoxin A levels, food consumption, and risk biomarkers of a representative sample of men and women from the Molise region in Italy. Eur J Nutr 2012; 51: 851-60.

    OA was detected in 99.1% of 327 asymptomatic patients. 5.2% exceeded 500 ng/L (**NB**: look at these data!). Mutton, lamb, cereal, wine, beer and jam/honey were correlated with OA levels.

15. Marin S, Ramos-A, Cano-Sancho G, Sanchis V. Mycotoxins: occurrence, toxicology, and exposure assessment. Food Chem Toxicol 2013; 60: 218-37.

    Mycotoxins are abiotic hazards produced by certain fungi that grow on a variety of crops. Their prevalence in plant raw materials may be high

16. Wu F, Groopman J, Pestka J. Public health impacts of foodborne mycotoxins. Annu Rev Food Sci Technol 2014; 5: 351-72.

Attempts to estimate global burden of disease caused by dietary exposure.

17. Mycotoxins and human health. IARC Sci Publ 2012; 158: 87-104.

The full impact on human health of widespread exposure to mycotoxins remains to be defined. For OA and zearalenone the human health effects remain undefined.

18. Stoll D, Schmidt-Heydt M, Geisen R. Differences in the regulation of ochratoxin A by the HOG pathway in Penicillium and Aspergillus in response to high osmolar environments. Toxins 2013; 5: 1282-98.

Both NaCl and sugar can impact on survival of OA formers.

19. Kuiper-Goodman T, Scott P. Risk assessment of the mycotoxin ochratoxin A. Biomed Environ Sci 1989; 3: 179-248.

83% of 233 asymptomatic patients showed OA in first morning urine, with mean of 14 ng/g creatinine. Maximum was 75.6 ng/g creatinine.

20. Akdemir C, Ulker O, Basaran A, Ozkaya S, Karakaya A. Estimation of ochratoxin A in some Turkish populations: an analysis in urine as a simple, sensitive and reliable biomarker. Food Chem Toxicol 2010; 48: 877-82.

21. Coronel M, Marin S, Tarrago M, Cano-Sancho G, Ramos A, Sanchis V. Ochratoxin A and its metabolite ochratoxin alpha in urine and assessment of the exposure of inhabitants of Lleida, Spain. Food Chem Toxicol 2011; 49: 1436-42.

72 asymptomatic patients were analyzed by HPLC for OA in urine. OA metabolite ochratoxin alpha was higher than OA with more OA alpha found with a three day food diary compared to a one day diary.

22. Manique R, Pena A, Lino C, Molto J, Manes J. Ochratoxin A in the morning and afternoon portions of urine from Coimbra and Valencian populations. Toxicon 2008; 51: 1281-7.

121 samples from asymptomatic patients from two sites in Iberia, with afternoon urine concentration far higher than AM samples, with levels exceeding 0.12 ng/ml (12 ppb).

23. Pena A, Seifrtova M, Lino C, Silveira I, Solich P. Estimation of ochratoxin A in Portuguese population: new data on the occurrence in human urine by high performance liquid chromatography with fluorescence detection. Food ChemToxicol 2006; 44: 1449-54.

OA conjugation with glucuronic acid occurs in human urine. Levels of OA again are found to exceed 0.1 ng/ml (10 ppb).

24. Sizoo E, van Egmond H. Analysis of duplicate 24-hour diet samples for aflatoxin B1, aflatoxin M1 and ochratoxin A. Food Addit Contam 2005; 22: 163-72.

123 samples were examined for aflatoxins and OA. M1 was found in 48% of samples. B1 42% and OA 100%. Dietary assessment showed no risk of calculated intake of 1.2 ng/kg bw/day despite positive urine findings.

25. Gilbert J, Brereton P, MacDonald S. Assessment of dietary exposure to ochratoxin A in the UK using a duplicate diet approach and analysis of urine and plasma samples. Food Addit Contam 2001; 18: 1088-93.

50 individuals provided urine and blood samples over 30 days. OA was found in all plasma samples and 46 of 50 urine samples. A significant correlation of urine OA and dietary OA consumption was demonstrated. Urine testing can show exposure to dietary OA.

26. Palli D, Miraglia M, Calogero S, Masala G, Cava E, Colatosti M, Coris A, Russo A, Brera C. Cancer Epi, Biomarkers and Preven 1999; 8: 265-269. Serum levels of ochratoxin A in healthy adults in Tuscany: correlation with individual characteristics and between repeat measurements.

OA levels were measured in serum in 138 healthy patients. All but 4 were positive. Mean values were 0.56 ng/ml (560 ppb). Summer values were higher than autumn. A subgroup of patients was tested one year later showing no significant correlation from year to year. "OA levels are a short-term biomarker with a high within-subject variability; therefore they have limited use at the individual level but can be used to characterize populations."

What can we learn from these papers? OA is easy to find in urine though ELISA is too non-specific to ever be used. Urinary OA has no correlation with any illness as controls with both high and low levels remained well. There is clear evidence that OA is present in foods eaten by nearly everyone. There is no question that urine of just about everyone will show levels of OA that are measurably much higher than those reported to be found in CFS and sinusitis patients.

The role of activity of water is again demonstrated. If the activity of water is less than 0.80, there will be no manufacture of mycotoxins.

Mycotoxin biosynthesis is coordinated activation of specific genes that are homologous between multiple mycotoxins and across species. Environmental stimuli including rainfall and temperature are involved with regulation of the biosynthesis pathways