

December 31, 2018

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Professor of Medical Science

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**Research Interests:** *Chemical Carcinogenesis, Molecular Oncology*

- DNA damage, DNA repair and mutagenesis
- Mechanisms of carcinogenicity and toxicity of metals and formaldehyde
- Cell death and resistance mechanisms for carcinogens and DNA-targeting cancer drugs
- Role of ascorbate in metabolism and toxicity of drugs and carcinogens

**Education**

**B.Sc.** (with distinction) - 1984 (biochemistry), Belarusian State University, Minsk, Belarus  
**Ph.D.** - 1989 (biochemistry), Belarusian Academy of Science, Belarus

**Faculty Appointments**

2010 *Professor*, Brown University, Dept. of Pathology and Laboratory Medicine  
2004 *Associate Professor* (with tenure), Brown University, Dept. of Pathology and Lab. Medicine  
1998 *Assistant Professor* (tenure-track), Brown University, Dept. of Pathology and Lab. Medicine  
1997 *Assistant Professor* (tenure-track), NYU, Dept. of Environmental Medicine  
1993 *Research Assistant Professor*, NYU, Dept. of Environmental Medicine

**Postdoctoral Positions**

1991-93 *Research Associate*, NYU, Dept. of Environmental Medicine  
1989-91 *Researcher*, Institute of Radiobiology, Minsk, Belarus

**Awards/Honors**

- *1<sup>st</sup> place award*, Team of Belarus, Undergraduate Competition in Biology (Kishinev, Moldova, 1983)
- *2<sup>nd</sup> place award (in biochemistry)*, National Undergraduate Research Conference (Novosibirsk, Russia, 1984)
- *Medal from the government of Belarus* for work in Chernobyl accident-contaminated areas (1991)
- *Manning Assistant Professor* (2000-2004)
- *Dean's Teaching Excellence Award* (2004, 2006, 2007, 2008) – Medical School teaching
- *Certificate of Recognition for Exemplary Teaching* (2009) - Medical School teaching
- *Nelson Fausto Teaching Award* (2009, inaugural award) - Undergraduate teaching
- *Dean's Excellence in Teaching Award* (2010) - Medical School teaching
- *Certificate of Recognition for Exemplary Teaching* (2011) - Medical School teaching
- *Dean's Excellence in Teaching Award* (2012) - Medical School teaching
- *Certificate of Recognition for Exemplary Teaching* (2013) - Medical School teaching
- *Dean's Excellence in Teaching Award* (2014) - Medical School teaching
- *Certificate of Recognition for Exemplary Teaching* (2015) - Medical School teaching
- *Dean's Excellence in Teaching Award* (2016) - Medical School teaching

- *William J. Waddell seminar*, Dept. of Pharmacology and Toxicology, University of Louisville School of Medicine, KY (May, 2016)
- *Keynote Lecture*, 9<sup>th</sup> Conference on Metal Toxicity and Carcinogenesis, Lexington, KY (Oct. 16-19, 2016)
- *Certificate of Recognition for Exemplary Teaching* (2017) - Medical School teaching
- *Office of Medical Education Letter of Recognition* (2018)

### **Professional Activities**

- *Councilor*, Metals Specialty Section, Society of Toxicology (2001-2003)
- *Biomonitoring Scientific Advisory Board*, Rhode Island Dept. of Health (2002-2003)
- *Organizer and co-Chair*, Symposium on *Metal Carcinogenesis: New Concepts* (2006)
- *Editorial Board*, 10th International Symposium on Metal Ions in Biology and Medicine (2008)
- *Ph.D. Jury*, University of Coimbra, Portugal (2009)
- *NIH study section XNDA* – regular member (2006-2010)
- *Organizing Committee* – 6<sup>th</sup> Conference on Metal Toxicity and Carcinogenesis (2010)
- *Executive Committee*, Division of Chemical Toxicology, American Chemical Society (2008-2011)
- *Chair, Peer Review Workshop* for EPA’s Toxicological Review of Hexavalent Chromium (2011)
- *Editorial Board, Chemical Research in Toxicology* (2007-2012)
- *Scientific Advisory Board*, NanoMedicine Research, Ltd (2008 – 2010)
- *Organizing Committee* – 7<sup>th</sup> Conference on Metal Toxicity and Carcinogenesis (2012)
- *Consultant*, Lynntech Inc, SBIR Phase I award from the U.S. Air Force (8/2012- 5/2013)
- Editorial Advisory Board member, *Chemical Research in Toxicology* (2014-present)
- Member, Peer Review Panel for the National Toxicology Program (NTP) Report on Carcinogens: Monograph on Cobalt and Certain Cobalt Compounds (July 22, 2015)
- NIH Study Section SIEE, regular member (7/1/15-6/30/19)
- *Grant reviewer – ad hoc* (20 NIH panels, 8 other agencies/organizations)
  - 2000 - Canadian Research Council
  - 2002 - NIH study section ALTX-1
  - 2003 - NIOSH intramural grant proposals
    - NIEHS Center at Vanderbilt University
  - 2004 - NIH study section ZAT1
    - NIH Study Section XNDA
    - Welcome Trust, Molecular and Cell Biology Panel, UK
  - 2005 - NIH study section ZRG1 DIG-F
    - NIH Study Section XNDA
    - NIH Study Section ZRG1 ONC-B
    - NIOSH intramural grant proposals
  - 2006 - NIH study section XNDA
    - NIH Study Section CE (two meetings)
    - NIH Study Section ZRG1 ONC-T
  - 2007 - Austrian Science Fund
  - 2009 - NIH Study Section ZRG1 OBT-S (02) M
  - 2010 - NIH Study Section ZRG1 DKUS-F 03
  - 2011 - NIH Study Section ZRG1 OBT-H (02) M
  - 2012 - NIH Study Section ZES1 JAB-D (V)
    - NIEHS Center at University of Arizona
  - 2013 - NIH Study Section SIEE (two meetings)
  - 2014 - NIH Study Section SIEE
  - 2015 - NIH Study section SIEE

- NIH Study section CE
  - Partnership for Native American Cancer Prevention, University of Northern Arizona
- 2016 - NIH Study Section ZES1 JAB-J (TS)

## 2017

- Editorial Advisory Board member, *Chemical Research in Toxicology*
- NIH Study Section SIEE, regular member

## 2018

- Editorial Advisory Board member, *Chemical Research in Toxicology*
- NIH Study Section SIEE, regular member

### Professional Societies

1. AAAS (*American Association for Advancement of Science*)
2. AACR (*American Association for Cancer Research*)
3. ACS (*American Chemical Society*)
4. EMGS (*Environmental Mutagenesis and Genomics Society*)
5. SOT (*Society of Toxicology*)

### Brown University Service

- *Freshmen Advisor* (2002-2003)
- *Biology Concentration Advisor* (2007 - present)
- *Pathobiology Graduate Program committees:*
  - Steering (1999-2010)
  - Seminar series, chair (2003, 2007)
  - Retreat, chair (2000, 2001)
  - Admission (1999, 2000 co-chair)
  - Award committee, chair (2008)
- *Faculty Search Committees*
  - 2002-2006
  - 2011-2012
  - 2013-2014 (chair)
  - 2017-2018
- *Grant reviewer:*
  - Salomon research grants (2006, 2009, 2016)
  - RIH COBRE Center for Cancer Research Development, Pilot projects (2005, 2007)
  - Brown-MBL Seed Projects (2010)
  - Pilot Projects in Translational Research (2010)
  - Research Fund Seed Proposals (2012)
  - COBRE CCRD pilot project grants (2015)
- *Presenter and Panelist*, “Navigating the Publication Process” workshop (2010)
- *EPSCoR PhD Fellowship Award Committee* (2011, 2012, 2013)
- *BioMed Space Policy Committee* (2011- 2012)
- *Strategic Planning Group* for Brown Program in Biology (2012)
- *Chair, Faculty Search Committee* (2012/2013)
- *Biology Research Space Committee* member (2013 - present)
- *Selection Committee*, Dean's Faculty Award in Grad & Postdoc Teaching and Mentoring (2013)

- *Departmental Mentor for Dr. Thomas Bartnikas, Assistant Professor (2013- present)*
- *Faculty Teaching-Mentoring Award Committee (2015, 2016)*
- *BioMed Division Mentor for Dr. Michelle Dawson, Assistant Professor (2016- present)*
- *Responsible Conduct in Research Training for BioMed graduate students, presenter for a section on Conflict of Interest*

## 2017

- *Biology Research Space Committee*
- *Faculty Search Committee*
- *Departmental Manager Search Committee*
- *PhD Committees for 5 students*
- *Departmental Mentor for Dr. Thomas Bartnikas, Assistant Professor*
- *BioMed Division Junior Faculty Mentor for Dr. Michelle Dawson, Assistant Professor in MPPB*

## 2018

- *Biology Research Space Committee*
- *Faculty Search Committee*
- *Faculty Promotion Committee*
- *Review Panel, FY19 Core Research Facility Infrastructure Applications*
- *PhD Committees for 4 students*
- *Departmental Mentor for Dr. Thomas Bartnikas, Assistant Professor*
- *BioMed Division Junior Faculty Mentor for Dr. Michelle Dawson, Assistant Professor in the Dept. of Molecular Pharmacology, Physiology and Biotechnology*
- *COBRE Mentoring committee for Dr. Patrycja Dubielecka, Assistant Professor of Medicine*

## Journal Publications

(peer-reviewed)

1. Konoplya EF, Detinkin ON and Zhitkovich AV. Age-related changes of the glucocorticoid-receptor complex translocation and initiation of RNA synthesis in liver cell nuclei. *Vesti AN BSSR, ser. biol. nauk* 2: 75-79 (1987).
2. Konoplya EF, Detinkin ON and Zhitkovich AV. Study of age peculiarities of the structural state of the chromatin of rat liver cells using micrococcal nuclease and circular dichroism. *Biokhimiia (Biochemistry-Moscow)* 53: 1614-1619 (1988).
3. Konoplya EF and Zhitkovich AV. Changes of the rat liver chromatin in aging. *Vesti AN BSSR, ser. biol. nauk* 5:54-58 (1988).
4. Konoplya EF, Detinkin ON and Zhitkovitch AV. Increase in content of tightly bound complexes of DNA-protein in rat liver cell nuclei with aging. *Vopr. Med. Khim.* 35: 78-82 (1989).
5. Yegutkin GG and Zhitkovich AV. Assessment of age-related changes in the structural state of plasma membranes from rat adipose tissue using the method of inductive-resonance energy transfer. *Nauchnye Dokl. Vyss. Shkoly Biol. Nauki* 8: 30-38 (1990).
6. Konoplya EF, Bulanova KJ, Zhitkovich AV, Miliutin AA, Kiriluk AP. Lipid composition of cardiomyocyte sarcolemma in rats of various age. *Vesti AN BSSR, seria biol. nauk* 2: 88-92 (1990).

7. Konoplya EF, Luksha GL, Detinkin ON, Zhitkovich AV, Gavrilin MA, Montik VI, Fil'tchenkov GN. The mechanism of transduction of glucocorticoid effects in ageing. *Fiziol. Zh. SSSR Im. IM Sechenova* 76: 1224-1230 (1990).
8. Yegutkin GG, Sambursky SS, Zhitkovitch AV and Gatsko GG. Evaluation of age-related changes of physicochemical properties and functional activity of rat adipose plasma membranes and their possible relationship. *Mech. Ageing Dev.* 59: 1-16 (1991).
9. Yanushevsky DS, Konevalova NJ, Zhitkovich AV, Detinkin ON and Chirkin AA. Effect of low dose ionizing irradiation on lipid transportation and cholesterol esterification in blood and subfraction composition of histone H1 from rat liver chromatin: correlation with age-related changes. *Vesti AN BSSR, seria biol. nauk* 3-4: 46-50 (1992).
10. Konoplya EF, Voitkun VA, Zhitkovich AV and Miliutin AA. Effect of phorbol esters and amiloride on the radiation-induced interphase death of thymocytes. *Dokl. Akad. Nauk* 324: 452-455 (1992).
11. Zhitkovich A and Costa M. A simple sensitive assay to detect DNA-protein crosslinks in intact cells and in vivo. *Carcinogenesis* 13: 1485-1489 (1992).
12. Salnikow K, Zhitkovich A and Costa M. Analysis of the binding sites of chromium to DNA and protein in vitro and in intact cells. *Carcinogenesis* 13: 2341-2346 (1992).
13. Lipskaya LA, Zhitkovich AV, Vasyukhin VI, Tsvetkov AG and Salnikow KV. The participation of endonuclease in the formation of extrachromosomal DNA and the possible mechanisms of gene amplification. *Tsitologiya* 35: 70-78 (1993).
14. Costa M, Zhitkovich A and Toniolo P. DNA-protein crosslinks in welders: molecular implications. *Cancer Res.* 53: 460-463 (1993).
15. Kargacin B., Squibb K.S., Cosentino S., Zhitkovich A. and Costa M. Comparison of the uptake and distribution of chromium in rats and mice. *Biol. Trace Element Res.* 36: 307-318 (1993).
16. Taioli E, Kinney P, Zhitkovich A, Fulton H, Voitkun V, Cosma G, Frenkel K, Toniolo P, Garte S and Costa M. Application of reliability models to studies of biomarker validation. *Environ. Health Perspect.* 102: 306-309 (1994).
17. Voitkun V, Zhitkovich A and Costa M. Complexing of amino acids to DNA by chromate in intact cells. *Environ. Health Perspect.* 102 (suppl. 3): 251-255 (1994).
18. Zhitkovich A, Voitkun V and Costa M. Glutathione and free amino acids form stable adducts with DNA following exposure of intact mammalian cells to chromate. *Carcinogenesis* 16: 907-913 (1995).
19. Taioli E, Zhitkovich A, Toniolo P, Costa M. Normal values of DNA-protein crosslinks in mononuclear cells of a population of healthy controls. *Cancer J.* 8: 76-78 (1995).
20. Lee Y-W, Klein CB, Kargacin B, Salnikow K, Kitahara J, Dowjat K, Zhitkovich A, Christie NT and Costa M. Carcinogenic nickel silences gene expression by chromatin condensation and DNA methylation: a new model for epigenetic carcinogens. *Mol. Cell. Biol.* 15: 2547-2557(1995).

21. Huang X, Kitahara J, Zhitkovich A, Dowjat K and Costa M. Heterochromatic proteins specifically enhance nickel-induced 8-oxo-dG formation. *Carcinogenesis* 16: 1753-1759 (1995).
22. Taioli E, Zhitkovich A, Kinney P, Udasin I, Toniolo P and Costa M. Increased DNA-protein crosslinks in lymphocytes of residents living in chromium contaminated areas. *Biol. Trace Element Res.* 50: 175-180 (1995).
23. Taioli E, Zhitkovich A, Toniolo P, Bernstein J, Blum R, Costa M. DNA-protein crosslinks as a biomarker of cis-platinum activity in cancer patients. *Oncol. Rep.* 3: 439-441 (1996).
24. Zhitkovich A, Lukanova A, Popov T, Taioli E, Cohen H, Costa M and Toniolo P. DNA-protein crosslinks in peripheral lymphocytes of individuals exposed to hexavalent chromium compounds. *Biomarkers* 1: 86-93 (1996).
25. Zhitkovich A, Voitkun V and Costa M. Formation of the amino acid-DNA complexes by hexavalent and trivalent chromium in vitro: importance of trivalent chromium and the phosphate group. *Biochemistry* 35: 7275-7282 (1996).
26. Costa M, Zhitkovich A, Gargas M, Paustenbach D, Finley B, Kuykendall J, Billings R, Carlson T, Wetterhahn K, Xu J, Patierno S, Bogdanffy M. Interlaboratory validation of a new assay for DNA-protein crosslinks. *Mutat. Res.* 369: 13-21 (1996).
27. Costa M, Zhitkovich A, Toniolo P, Taioli E, Popov T and Lukanova A. Monitoring of human lymphocytic DNA-protein crosslinks as a biomarker of biologically active doses of chromate. *Environ. Health Perspect.* 104 (suppl. 5): 917-919 (1996).
28. Lukanova A, Toniolo P, Zhitkovich A, Nikolova V, Panev T, Popov T, Taioli E and Costa M. Occupational exposure to Cr(VI): comparison between chromium levels in lymphocytes, erythrocytes and urine. *Int. Arch. Occup. Environ. Health* 69: 39-44 (1996).
29. Costa M, Zhitkovich A, Harris M, Paustenbach D and Gargas M. DNA-protein crosslinks produced by various chemicals in cultured human lymphoma cells. *J. Toxicol. Environ. Health* 50: 433-449 (1997).
30. Voitkun V, Zhitkovich A and Costa M. Cr(III)-mediated crosslinks of glutathione or amino acids to the DNA phosphate backbone are mutagenic in human cells. *Nucleic Acids Res.* 26: 2024-2030 (1998).
31. Zhitkovich A, Voitkun V, Kluz T and Costa M. Utilization of DNA-protein crosslinks as a biomarker of chromium exposure. *Environ. Health Perspect.* 106 (suppl. 4): 969-974 (1998).
32. Voitkun V and Zhitkovich A. Analysis of DNA-protein crosslinking activity of malondialdehyde in vitro. *Mutation Research*, 424: 97-106 (1999).
33. Sutherland JE, Zhitkovich A, Kluz T and Costa M. Rats retain chromium in tissues following chronic ingestion of drinking water containing 3 or 10 ppm hexavalent chromium. *Biol. Trace Element Res.* 74: 41-53 (2000).
34. Quievryn G and Zhitkovich A. Loss of DNA-protein crosslinks from formaldehyde-exposed cells occurs through spontaneous hydrolysis and an active repair process linked to proteasome function. *Carcinogenesis* 21: 1573-1580 (2000).

35. Zhitkovich A, Messer J and Shrager S. Reductive metabolism of Cr(VI) by cysteine leads to the formation of binary and ternary Cr-DNA adducts in the absence of oxidative DNA damage. *Chem. Res. Toxicol.* 13: 1114-1124 (2000).
36. Zhitkovich A, Song Y, Quievryn G and Voitkun V. Non-oxidative mechanisms are responsible for the induction of mutagenesis by reduction of Cr(VI) with cysteine: role of ternary DNA adducts in Cr(III)-dependent mutagenesis. *Biochemistry* 40: 549-560 (2001).
37. Quievryn G, Goulart M, Messer J and Zhitkovich A. Reduction of Cr(VI) by cysteine: significance in human lymphocytes and formation of DNA damage in reactions with variable reduction rates. *Mol. Cell. Biochem.* 222: 107-118 (2001).
38. Quievryn G, Messer J and Zhitkovich A. Carcinogenic chromium(VI) induces cross-linking of vitamin C to DNA *in vitro* and in human lung A549 cells. *Biochemistry* 41: 3156-3167 (2002).
39. Zhitkovich A, Quievryn G, Messer J and Motylevich Z. Reductive activation with cysteine represents a chromium(III)-dependent pathway in the induction of genotoxicity by carcinogenic chromium(VI). *Environ. Health Perspect.* 110: 729-731 (2002).
40. Medeiros MG, Rodrigues AS, Batoreu MC, Laires A, Rueff J and Zhitkovich A. Elevated levels of DNA-protein crosslinks and micronuclei in peripheral lymphocytes of tannery workers exposed to trivalent chromium. *Mutagenesis* 18: 19-24 (2003).
41. Quievryn G, Peterson E, Messer J and Zhitkovich A. Genotoxicity and mutagenicity of chromium(VI)/ascorbate-generated DNA adducts in human and bacterial cells. *Biochemistry* 42: 1062-1070 (2003).
42. Dickinson DA, Warnes GR, Quievryn G, Messer J, Zhitkovich A, Rubitski E and Aubrecht J. Differentiating DNA-reactive and non-reactive genotoxic mechanisms using gene expression profile analysis. *Mutat. Res.* 549: 29-41 (2004).
43. Reynolds M, Peterson E, Quievryn G and Zhitkovich A. Human nucleotide excision repair efficiently removes DNA phosphate-chromium adducts and protects cells against chromate toxicity. *J. Biol. Chem.* 279: 30419-30424 (2004).
44. Salnikow K, Donald SP, Bruick RK, Zhitkovich A, Phang JM and Kasprzak KS. Depletion of intracellular ascorbate by the carcinogenic metals nickel and cobalt results in the induction of hypoxic stress. *J. Biol. Chem.* 279: 40337-40344 (2004).
45. Zhitkovich A. Importance of chromium-DNA adducts in mutagenicity and toxicity of chromium(VI). *Chem. Res. Toxicol.* 18: 3-11 (2005).  
\* **Journal Cover** (January issue)  
\***#1 downloaded paper for 2005**
46. Peterson-Roth E, Reynolds M, Quievryn G and Zhitkovich A. Mismatch repair proteins are activators of toxic responses to chromium-DNA damage. *Mol. Cell. Biol.* 25: 3596-3607 (2005). PMC1084304
47. Zhitkovich A, Peterson-Roth E, Reynolds M. Killing of chromium-damaged cells by mismatch repair and its relevance to carcinogenesis. *Cell Cycle* 4: 1050-1052 (2005).

48. Karaczyn A, Ivanov S, Reynolds M, Zhitkovich A, Kasprzak KS and Salnikow K. Ascorbate depletion mediates up-regulation of hypoxia-associated proteins by cell density and nickel. *J. Cell. Biochem.* 97: 1025-1035 (2006).
49. Messer J, Reynolds M, Stoddard L and Zhitkovich A. Causes of DNA single-strand breaks during reduction of chromate by glutathione in vitro and in cells. *Free Radic. Biol. Med.* 40: 1981-1992 (2006).
50. Quievryn G, Messer J and Zhitkovich A. Lower mutagenicity but higher stability of Cr-DNA adducts formed during gradual chromate activation with ascorbate. *Carcinogenesis* 27: 2316-2321 (2006).
51. Reynolds M, Stoddard L, Bepalov I and Zhitkovich A. Ascorbate acts as a highly potent inducer of chromate mutagenesis and clastogenesis: linkage to DNA breaks in G2 phase by mismatch repair. *Nucleic Acids Res.* 35: 465-476 (2007). PMC1802609  
\* **Brown University press release** (3/12/2007)  
\* **NIH-NIEHS Research Briefs** (April 2007)  
\* **EnviroNews: "Mutagenic mix"**. *Environ. Health Perspect.* 115 (7), p. A349 (2007)  
\* **Highlighted accomplishment**, Brown Division of Biology and Medicine, 2008-2009 Annual Report
52. Reynolds M and Zhitkovich A. Cellular vitamin C increases chromate toxicity via a death program requiring mismatch repair but not p53. *Carcinogenesis* 28: 1613-1620 (2007).
53. Liu X, Gurel V, Morris D, Murray D, Zhitkovich A, Kane AB and Hurt RH. Bioavailability of nickel in single-wall carbon nanotubes. *Advanced Materials* 19: 2790-2796 (2007).
54. Salnikow K and Zhitkovich A. Genetic and epigenetic mechanisms in metal carcinogenesis and cocarcinogenesis: nickel, arsenic and chromium. *Chem. Res. Toxicol.* 21: 28-44 (2008). PMC2602826  
\***#2 downloaded paper for 2008**  
\* **Highly Cited Paper** (top 1% cited paper in pharmacology/toxicology, Web of Science)
55. Branco R, Chung AP, Johnston T, Gurel V, Morais P and Zhitkovich A. Chromate-inducible *chrBACF* operon from transposable element *TnOtChr* confers resistance to chromium(VI) and superoxide. *J. Bacteriol.* 190: 6996-7003 (2008). PMC2580707  
\***News report** in *NIH-NIEHS e-Posted Notes*. November 5, 2008 (Issue 59)
56. Guttman D, Poage G, Johnston T and Zhitkovich A. Reduction with glutathione is a weakly mutagenic pathway in chromium(VI) metabolism. *Chem. Res. Toxicol.* 21: 2188-2194 (2008). PMC2665875
57. Reynolds MF, Peterson-Roth EC, Johnston T, Gurel VM, Menard HL and Zhitkovich A. Rapid DNA double-strand breaks resulting from processing of Cr-DNA crosslinks by both MutS dimers. *Cancer Res.* 69: 1071-1079 (2009). PMC3226787  
\***Spotlight**: "Cr-DNA lesion misrepair". *Chem. Res. Toxicol.* 22 (4), p. 608 (2009)
58. Zecevic A, Menard H, Gurel V, Hagan E, DeCaro R and Zhitkovich A. WRN helicase promotes repair of DNA double-strand breaks caused by aberrant mismatch repair of chromium-DNA adducts. *Cell Cycle* 8: 2769-2778 (2009). PMC3226781
59. Macfie A, Hagan E and Zhitkovich A. Mechanism of DNA-protein cross-linking by chromium. *Chem. Res. Toxicol.* 23: 341-347 (2010). PMC2822107  
\* **Editorial Highlight** "In this Issue"  
\* **Highlighted research in the testimony by the Director of NIEHS before the Senate Committee on**



**Environmental and Public Works (February 2, 2011)**

60. Zecevic A, Hagan E, Reynolds M, Poage G, Johnston T and Zhitkovich A. XPA impacts formation but not proteasome-sensitive repair of DNA-protein crosslinks induced by chromate. *Mutagenesis* 25: 381-388 (2010). PMC2893307
61. Pietruska JR, Johnston T, Zhitkovich A, Kane AB. XRCC1 deficiency sensitizes human lung epithelial cells to genotoxicity by crocidolite asbestos and Libby amphibole. *Environ. Health Perspect.* 118: 1707-1713 (2010). PMC3205592
62. Zhitkovich A. Chromium in drinking water: sources, metabolism, and cancer risks. *Chem. Res. Toxicol.* 24: 1617-1629 (2011). PMC3196244  
\* **Journal Cover** (October issue)  
\* **Highly Cited Paper** (top 1% cited paper in pharmacology/toxicology, Web of Science)
63. Pietruska JR, Liu X, Smith A, McNeil K, Weston P, Zhitkovich A, Hurt R, Kane AB. Bioavailability, intracellular mobilization of nickel, and HIF-1 $\alpha$  activation in human lung epithelial cells exposed to metallic nickel and nickel oxide nanoparticles. *Toxicol. Sci.* 124: 138-148 (2011). PMC3196652
64. Reynolds M, Armknecht S, Johnston T and Zhitkovich A. Undetectable role of oxidative DNA damage in cell cycle, cytotoxic and clastogenic effects of Cr(VI) in human lung cells with restored ascorbate levels. *Mutagenesis* 27: 437-443 (2012). PMC3382305
65. Wong V, Armknecht S and Zhitkovich A. Metabolism of Cr(VI) by ascorbate but not glutathione is a low oxidant-generating process. *J. Trace Elem. Med. Biol.* 26: 192-196 (2012). PMC3380165
66. Wong VC, Cash HL, Morse JL, Lu S and Zhitkovich A. S-phase sensing of DNA-protein crosslinks triggers TopBP1-independent ATR activation and p53-mediated cell death by formaldehyde. *Cell Cycle* 11: 2526-2537 (2012). PMC3404879
67. Wong VC, Morse JL and Zhitkovich A. p53 activation by Ni(II) is a HIF-1 $\alpha$  independent response causing caspases 9/3-mediated apoptosis in human lung cells. *Toxicol. Appl. Pharmacol.* 269: 233-239 (2013). PMC3666101
68. Morse JL, Luczak MW and Zhitkovich A. Chromium(VI) causes interstrand DNA cross-linking in vitro but shows no hypersensitivity in cross-link repair-deficient human cells. *Chem. Res. Toxicol.* 26: 1591-1598 (2013). PMC3838998
69. Luczak MW and Zhitkovich A. Role of direct reactivity with metals in chemoprotection by N-acetylcysteine against chromium(VI), cadmium(II) and cobalt(II). *Free Radic. Biol. Med.* 65: 262-269 (2013). PMC3823631
70. Green SE, Luczak MW, Morse JL, DeLoughery Z and Zhitkovich A. Uptake, p53 pathway activation and cytotoxic responses for Co(II) and Ni(II) in human lung cells: implications for carcinogenicity. *Toxicol. Sci.* 136: 467-477 (2013). PMC3858198
71. DeLoughery Z, Luczak MW and Zhitkovich A. Monitoring Cr intermediates and reactive oxygen species with fluorescent probes during chromate reduction. *Chem. Res. Toxicol.* 27: 843-851 (2014). PMC4027954

72. DeLoughery Z, Luczak MW, Ortega-Atienza S and Zhitkovich A. DNA double-strand breaks by Cr(VI) are targeted to euchromatin and cause ATR-dependent phosphorylation of histone H2AX and its ubiquitination. *Toxicol. Sci.* 143: 54-63 (2015). PMC4274381  
\***Journal Cover** (January issue)
73. Ortega-Atienza S, Green SE and Zhitkovich A. Proteasome activity is important for replication recovery, CHK1 phosphorylation and prevention of G2 arrest after low-dose formaldehyde. *Toxicol. Appl. Pharmacol.* 286: 135-141 (2015). PMC4458209
74. Sawant A, Kothandapani A, Sobol RW, Zhitkovich A and Patrick SM. Role of mismatch repair proteins in the processing of cisplatin interstrand cross-links. *DNA Repair* 35: 126-136 (2015). PMC4651805
75. Luczak MW, Green SE and Zhitkovich A. Different ATM signaling in response to chromium(VI) metabolism via ascorbate and nonascorbate reduction: implications for in vitro models and toxicogenomics. *Environ. Health Perspect.* 124: 61-66 (2016). PMC4710604
76. Ortega-Atienza S, Wong VC, DeLoughery Z, Luczak MW and Zhitkovich A. ATM and KAT5 safeguard replicating chromatin against formaldehyde damage. *Nucleic Acids Res.* 44: 198-209 (2016). PMC4705693
77. Ortega-Atienza S, Rubis B, McCarthy C. and Zhitkovich A. Formaldehyde is a potent proteotoxic stressor causing rapid heat shock transcription factor 1 activation and Lys48-linked polyubiquitination of proteins. *Am. J. Pathol.* 186: 2857-2868 (2016). PMC5222959  
\* **Brown news report** (Sept. 29, 2016)  
\* **Brown Daily Herald** (Oct. 6, 2016)
78. Ortega-Atienza S, Krawic C, Watts L, McCarthy C, Luczak MW and Zhitkovich A. 20S immunoproteasomes remove formaldehyde-damaged cytoplasmic proteins suppressing caspase-independent cell death. *Sci. Rep.* 7: 654 (2017). PMC5429636
79. Luczak MW and Zhitkovich A. Nickel-induced HIF-1 $\alpha$  promotes growth arrest and senescence in normal human cells but lacks toxic effects in transformed cells. *Toxicol. Appl. Pharmacol.* 331: 94-100 (2017). PMC5568485
80. Krawic C, Luczak MW and Zhitkovich A. Variation in extracellular detoxification is a link to different carcinogenicity among chromates in rodent and human lungs. *Chem. Res. Toxicol.* 30: 1720-1729 (2017). PMC5605882  
\* **ACS Editors' Choice article**  
\* **Journal Cover**
81. Luczak MW and Zhitkovich A. Monoubiquitinated  $\gamma$ -H2AX: Abundant product and specific biomarker for non-apoptotic DNA double-strand breaks. *Toxicol. Appl. Pharmacol.* 355: 238-246 (2018).
82. Krawic C and Zhitkovich A. Toxicological antagonism among welding fume metals: inactivation of soluble Cr(VI) by iron. *Chem. Res. Toxicol.* 31: 1172-1184 (2018). PMC6247247

## Book Chapters

1. Zhitkovich A. and Costa M. Biological markers. In: *Occupational and Environmental Medicine*. 3rd edition, pp. 177-186. W. Rom, ed.; Lippincott and Raven, Philadelphia (1998).
2. Zhitkovich A. Chromium: exposure, toxicity and biomonitoring approaches. In: *Biomarkers of Environmentally Associated Disease: Technologies, Concepts, and Perspectives*. Eds. S.H. Wilson, W.A. Suk. CRC Press, New York, pp. 267-285 (2002).
3. Zhitkovich A. Chromium binding to DNA. In: *Encyclopedia of Metalloproteins*. Eds. R.H. Kretsinger, V.N. Uversky, E.A. Permyakov; Springer Science, New York, pp.630-635 (2013).

### Meeting Proceedings

1. Zhitkovich A.V. and Detinkin O.N. Age-related changes in DNA-protein interaction in rat liver chromatin. In: *USSR symposium on Cell Biology*, Moscow. Vol. 1, pp. 273-275 (1985).
2. Zhitkovich A.V. Histone H1 subfractions and composition of non-histone proteins in liver cells from rats of different age. In: *17th Scientific Symposium of Young Investigators on Issues in Current Biology*, Moscow State University. Vol. 3, pp. 94-97 (1986).
3. Toniolo P., Zhitkovich A., Costa M. Development and utilization of a new simple assay for DNA-protein crosslinks as a biomarker of exposure to welding fumes. *Int. Arch. Occup. Environ. Health* 65: S87-S89 (1993).
4. Costa M, Zhitkovich A., Taioli E. and Toniolo P. Preliminary report on a simple new assay for DNA-protein cross-links as a biomarker of exposure experienced by welders. *J. Toxicol. Environ. Health*, 40: 217-222 (1993).
5. Zhitkovich A., Voitkun V., Song Y., Quievryn G. and DeLucia A. Chromium(III)-DNA adducts are the major form of mutagenic DNA lesions produced during reductive metabolism of chromate by cysteine. In: *Metal Ions in Biology and Medicine*, vol. 6, pp. 113-115. Eds. J. A. Centeno, Ph. Collery, G. Vernet, R. B. Finkelman, H. Gibb, J. C. Etienne. John Libbey Eurotext, Paris (2000).
6. Medeiros M.G., Rodrigues A.S., Batoreu M.C., Laires A., Zhitkovich A., Rueff J. Trivalent and hexavalent chromium exposure: a comparative study in tannery workers and welders. *Polish J. Environ. Studies*, 11 (suppl. II): 80-82 (2002).
7. Medeiros M.G., Rodrigues A.S., Batoreu M.C., Laires A., Zhitkovich A., Rueff J. Biomarkers of chromium exposure and cytogenetic damage in leather tanning and welding industry workers. In: *Human Biomonitoring for Genetic Effects* (A.C. Cebulska-Wasilewska, W.W. Au and R.J. Sram, eds), NATO Science Series I: Life and Behavioural Sciences, vol. 351, pp. 132-141, IOS Press (2003).
8. Quievryn G., Peterson E. and Zhitkovich A. Mutagenic DNA damage generated by chromium(VI) during its reductive activation with ascorbic acid. In: *Metal Ions in Biology and Medicine*, vol. 8, pp. 246-249. Eds. M.A. Cser, I. Sziklai Laszlo, J.-C. Etienne, Y. Maynard, J. Centeno, L. Khassanova, Ph. Collery. John Libbey Eurotext, Paris (2004).
9. Reynolds M. and Zhitkovich A. Ascorbate-mediated toxicity of hexavalent chromium in human cells. In: *Metal Ions in Biology and Medicine*, vol. 10, pp. 304-309. Eds. Ph. Collery, I. Maynard, L. Khassanova, T. Collery. John Libbey Eurotext, Paris (2008).

## **Commentaries**

Bartley E. and Zhitkovich A. Do not cross your DNA. *Chem. Res. Toxicol.* 21: 275 (2008).

## **Patents**

Costa M, Zhitkovich A. Assay for Detecting Covalent DNA-protein Complexes. U.S. patent N° 5545529. *Biotechnol. Adv.* 15(2): 410 (1997).

## **Invited Lectures**

1. 2<sup>nd</sup> International Meeting on Molecular Mechanisms of Metal Toxicity and Carcinogenicity, Madonna di Campiglio, Italy (1993).
2. Workshop on Biomarkers to Toxic and Carcinogenic Metals, Park City, Utah (1996)
3. Pathology Research Rounds, Brown University (1998)
4. Pathobiology Graduate Program, Brown University (1999)
5. University of Rhode Island, RI (2000)
6. International Conference on Arctic Development, Pollution and Biomarkers of Human Health. Anchorage, Alaska (2000)
7. Conference on Molecular Mechanisms of Metal Toxicity and Carcinogenesis. Morgantown, WV (2000)
8. Molecular and Cell Biology Graduate Program, Brown University (2000)
9. 3<sup>rd</sup> International Meeting on Molecular Mechanisms of Metal Toxicity and Carcinogenesis. Stintino, Italy (2001)
10. Pfizer, Inc. Groton, CT (2001)
11. 2<sup>nd</sup> Conference on Molecular Mechanisms of Metal Toxicity and Carcinogenesis. Morgantown, WV (2002)
12. Conference on Preventing Toxic Health Threats to Rhode Island Communities. Providence, RI (2002)
13. New York University School of Medicine (2003)
14. University of Texas Medical Branch, Galveston, TX (2003)
15. Lifespan COBRE Cancer Center, Providence, RI (2003)
16. National Cancer Institute, Frederick, MD (2003)
17. Vanderbilt University, Center in Molecular Toxicology, Nashville, TN (2003)
18. Pathology Research Rounds, Brown University (2003)
19. 3<sup>rd</sup> Conference on Molecular Mechanisms of Metal Toxicity and Carcinogenesis. Morgantown, WV (2004)

20. Gordon Research Conference on Genetic Toxicology. New London, NH (2005)
21. 232<sup>nd</sup> Annual Meeting of the American Chemical Society. San Francisco, CA (2006)
22. University of North Carolina, Chapel Hill, NC (2006)
23. Brown MCB Graduate Program, annual retreat (2007)
24. NUTMEG Conference, Woods Hole, MA (2007)
25. Miriam Hospital, Center for Behavioral and Preventive Medicine, Providence, RI (2007)
26. Superfund Basic Research Program: 20<sup>th</sup> anniversary conference, Durham, NC (2007)
27. 47<sup>th</sup> Annual Meeting of the Society of Toxicology, Seattle, WA (2008)
28. 236<sup>th</sup> Annual Meeting of the American Chemical Society, Philadelphia, PA (2008)
29. 5<sup>th</sup> Conference on Metal Toxicity and Carcinogenesis, Morgantown, WV (2008)
30. University of Connecticut, Storrs, PHAR-6455 Advanced Toxicology, 2-h lecture (2008)
31. University of Kentucky, Lexington (2008)
32. University of Pittsburgh (2009)
33. Pathology Research Rounds, Brown University (2009)
34. Wheeler School, Providence, RI (2010)
35. Rhode Island Hospital, Pathology Research Conference (2010)
36. 16<sup>th</sup> International Charles Heidelberger Symposium on Cancer Research, Portugal (2010)
37. 9<sup>th</sup> Meeting of International Society for Trace Elements Research in Humans, Turkey (October, 2011)
38. University of Connecticut, Storrs, PHAR-6455 Advanced Toxicology, 2-h lecture (November, 2011)
39. Michigan State University, East Lansing (September, 2012)
40. 7<sup>th</sup> Conference on Metal Toxicity and Carcinogenesis, Albuquerque, NM (October, 2012)
41. University of Arizona, Tucson (November, 2012)
42. 4<sup>th</sup> Georgian Bay International Conference on Bioinorganic Chemistry, Canada (May, 2013)
43. University of Connecticut, Storrs, PHAR-6455 Advanced Toxicology, 2-h lecture (October, 2013)
44. William J. Waddell seminar, Dept. of Pharmacology and Toxicology, University of Louisville School of Medicine, KY (May, 2016)
45. Annual retreat, Brown Graduate Program in Molecular Pharmacology and Physiology (May, 2016)
46. Keynote Lecture - 9<sup>th</sup> Conference on Metal Toxicity and Carcinogenesis, Lexington, KY (October 17, 2016)
47. University of Connecticut, Storrs, PHAR-6455 Advanced Toxicology, 2-h lecture (Nov. 11, 2016)
48. Tulane University Cancer Center (March 8, 2018)
49. Dept. of Toxicology and Cancer Biology, University of Kentucky, Lexington (April 30, 2018)
50. 10<sup>th</sup> Conference on Metal Toxicity and Carcinogenesis, Albuquerque, NM (October 29, 2018)

**Funding - current**  
Total grant cost: \$3.66 million

- 1) NIH R01 ES008786 "*Genotoxicity of Chromium Compounds*"  
Funding period: 4/1/15 - 1/31/20  
Role: PI  
Total cost: \$1,828K  
Direct cost: 1,125K  
Indirect cost: 703K
  
- 2) NIH R01 ES028072 "*Regulation of p53 and Checkpoint Signaling by Chromium(VI)*"  
Funding period: 12/1/17-11/30/22  
Role: PI  
Total cost: \$1,828K  
Direct cost: 1,125K  
Indirect cost: 703K
  
- 3) Gift from Lifespan, Division of Hematology and Oncology (to A. Zhitkovich)  
\$22,500

**Past Funding**  
Total cost: \$11.2 million

R01 grants (\$8.15 million)

- 1) ES008786 "*Genotoxicity of Chromium Compounds*"  
Funding period: 08/01/1997 - 07/31/2003  
Role: PI  
Total cost: \$1,134K
  
- 2) ES008786 "*Genotoxicity of Chromium Compounds*"  
Funding period: 9/23/2003 - 5/30/2009  
Role: PI  
Total cost: \$1,611K
  
- 3) ES012915 "*Sensitivity Mechanisms in Chromium Toxicity*"  
Funding period: 7/1/2004 – 5/31/2011  
Role: PI  
Total cost: \$1,584K
  
- 4) ES008786 "*Genotoxicity of Chromium Compounds*"  
Funding period: 06/01/09 - 3/31/15  
Role: PI  
Total cost: \$1.821K
  
- 5) NIH 1R01 ES020689 "*Formaldehyde Genotoxicity*"  
Funding period: 6/29/12 - 3/31/18

Role: PI  
Total cost: \$1,995K

### Program Projects (\$2.9 million)

- 1) P20-RR015578 “Center for Genetics and Genomics” (PI – J. Sedivy)  
Funding period: 9/1/2003 – 6/31/2004  
Role: Leader for Project “*Stress Signaling by DNA Methylation Damage*”  
Total cost: \$76K
- 2) P20 RR015578 “Cancer Signaling Networks” (PI – J. Sedivy)  
Funding period: 7/1/2005 - 4/30/2006  
Role: Leader of Project #5: “*Genetic Damage by Lipid Peroxidation*”  
Total cost for Project #5: \$175K
- 3) Superfund Basic Research Program P42 ES013660 “Reuse in RI: a State-Based Approach to Complex Exposures” (PI – K. Boekelheide).  
Funding period: 4/18/2005 – 3/31/2009  
Role: Leader of Project #4: “*Biological Dosimetry of Hexavalent Chromium*”  
Total cost for Project #4: \$1,279K
- 4) Superfund Research Program P42 ES013660 “Reuse in RI: a State-Based Approach to Complex Exposures” (PI – K. Boekelheide).  
Funding period: 4/1/2009 - 3/31/2014  
Role: Leader of Project #4: “*Biological Dosimetry of Hexavalent Chromium*”  
Total cost for Project #4: \$1,368K

### Contracts

U.S. Air Force SBIR Phase II Award No. FA8222-14-C-0004 “*Label-free Immunoassay-Based Assessment for Chromate Exposure.*” Subcontract from Lynntech Inc.  
Funding period: 10/6/14 - 7/22/15  
Role: PI for Brown subcontract  
Total cost: \$132K

### Small grants

- 1) Rhode Island Cancer Council, Transition Support Grant “*Role of DNA-Protein Crosslinks in Genotoxicity of Malondialdehyde*”.  
Funding period: 8/1/2001 – 12/31/2001  
Role: PI  
Total/direct cost: \$15K
- 2) NIH R13CA124263-01 “*Metal Carcinogenesis: New Concepts*”  
Funding period: 07/10/2006 - 07/09/2007  
Role: PI  
Total/direct cost: \$8K

### Internal grants

Brown Salomon Faculty Research Award “*Mutagenic Potential of DNA-Vitamin C Crosslinks*”

*Induced by Carcinogenic Hexavalent Chromium*". Funding period: 5/2002-12/2002  
Role: PI  
Direct cost: \$10K

### **Teaching**

Total number of courses taught: 19

#### Last 5 years teaching:

**2014** *Total lectures = 4.5 hrs*

- BIOL 3645 *General Pathology*, 4.5 lecture hrs
- *Fall Semester – sabbatical leave*

**2015** *Total lectures = 36 hrs*

- BIOL 1290 *Cancer Biology* (30 students), 31.5 lecture hrs, course director
- BIOL 3645 *General Pathology*, 4.5 lecture hrs
- BIOL1950 *Independent Studies*, 1 student (Sarah Pierce)

**2016** *Total lectures = 37 hrs*

- BIOL 1290 *Cancer Biology* (22 students), 30 lecture hrs, course director
- BIOL 3645 *General Pathology*, 4.5 lecture hrs
- BIOL 2170 *Molecular Pharmacology and Physiology*, 1.5 lecture hrs
- *Responsible Conduct in Research*, 1 lecture hr

**2017** *Total lectures = 34.5 hrs*

- BIOL 1290 *Cancer Biology* (28 students), 30 lecture hrs, course director
- BIOL 3645 *General Pathology*, 4.5 lecture hrs

**2018** *Total lectures = 4.5 hrs*

- BIOL 3645 *General Pathology*, 4.5 lecture hrs
- *Fall Semester – sabbatical leave*