

CITIZEN PETITION TO THE FOOD AND DRUG ADMINISTRATION

Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993

CENTER FOR FOOD SAFETY
660 Pennsylvania Ave, SE, Suite 302
Washington, DC 20003

**INSTITUTE FOR AGRICULTURE AND
TRADE POLICY,**
2105 First Avenue South
Minneapolis, MN 55404

et al.,

Petitioners,

v.

Docket Number _____

Filed With:

MARGARET A. HAMBURG, M.D.
In her official capacity as,
Commissioner of the Food and Drug
Administration

DOCKETS MANAGEMENT BRANCH
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

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CITIZEN PETITION SEEKING WITHDRAWAL OF APPROVAL OF ROXARSONE AND CERTAIN OTHER ARSENICAL ADDITIVES IN ANIMAL FEED

ACTIONS REQUESTED

Pursuant to the Right to petition the government clause contained in the First Amendment of the United States Constitution,¹ the Administrative Procedure Act,² and the Food and Drug Administration’s implementing regulations,³ Petitioners submit this citizen petition for rulemaking and collateral relief under the authority of §360b of the Federal Food, Drug, and Cosmetic Act (FDCA) to request the Commissioner of Food and Drugs to undertake the following actions:

(1) Immediately suspend the approval of all new animal drug applications (NADAs) for arsenic-containing compounds used as feed additives for food animals. The ban should include the arsenic-containing compounds:

- Roxarsone (3-nitro-4-hydroxyphenylarsonic acid)
- Arsanilic acid (p-arsanilic acid)
- Nitarsone (4-nitrophenylarsonic acid)
- Carbarsone (p-ureidophenylarsonic acid)

(2) Publish a Notice of Opportunity for an Evidentiary Hearing concerning “new evidence” related to these applications in accordance with 21 U.S.C. §512(e)(1).

¹ “Congress shall make no law ... abridging ... the right of the people ... to petition Government for a redress of grievances.” U.S.Const. amend. I. The right to “petition for redress of grievances is among the most precious of the liberties safeguarded by the Bill of Rights.” United Mine Workers of Am. Dist. 12 v. Ill. State Bar Ass’n, 389 U.S. 217, 222 (1967). It shares the “preferred place” accorded in our system of government to the First Amendment freedoms, and “has a sanctity and a sanction not permitting dubious intrusions.” Thomas v. Collins, 323 U.S. 516, 530 (1945). “[A]ny attempt to restrict those First Amendment liberties must be justified by the clear public interest, threatened not doubtful or remotely, but by clear and present danger.” *Id.* The Supreme Court has recognized that the right to petition is logically implicit in and fundamental to the very idea of a republican form of government. United States v. Cruikshank, 92 U.S. 542, 552 (1875).

² 5 U.S.C. §553(e) (2009).

³ 21 C.F.R. §§10.20, 10.30 (2009).

(3) Upon completion of the hearing, issue an order withdrawing the approval of all NADAs for arsenic-containing compounds used as feed additives for animals.

(4) Revoke all regulations associated with the approval of all NADAs for arsenic-containing compounds used as feed additives for animals, including those found at 21 C.F.R. §§558.62, 558.120, 558.369, 558.530.

PETITIONERS

The **Center for Food Safety** (CFS) is a Washington, D.C. based nonprofit located at 660 Pennsylvania Avenue, S.E., Washington D.C. 20003. Established in 1997, CFS works to protect human health and the environment by curbing the proliferation of harmful food production technologies and by promoting organic and other forms of sustainable agriculture.

The **Institute for Agriculture and Trade Policy** (IATP) is a 501(c)(3) organization located at 2105 First Avenue South, Minneapolis, MN 55404. Established in 1986, IATP works locally and globally at the intersection of policy and practice to ensure fair and sustainable food, farm and trade systems.

INTRODUCTION

In November 2009, U.S. Representative Steve Israel of New York announced legislation calling for a ban on the use of the arsenical compound roxarsone.⁴ This bill, known as the “Poison-Free Poultry Act of 2009” would prohibit all uses of roxarsone as a food additive in

⁴ Poison Free Poultry Act, H.R. 3624, 111th Cong. (2009); Press Release, Congressman Steve Israel, *What Carcinogens are in Your Turkey? Rep. Israel Announces New Legislation to Get Arsenic out of Poultry* (Nov. 23, 2009) (on file with author).

poultry.⁵ The introduction of this legislation illustrates the importance and urgency of the issue. Humans are exposed to arsenic from various pathways. Banning arsenic-containing compounds in feed additives would provide an easy solution to lighten the burden on public health. While the Poison-Free Poultry Act is a step in that direction, it would only ban roxarsone, the most widely used arsenic-containing compound. The Food and Drug Administration (FDA) can and should act to address this danger under its existing authority, by withdrawing all new animal drug applications (NADAs) for arsenic-containing compounds in animal feed.

Arsenic-containing compounds have been approved additives to food animal feed since the 1940s and are currently used in chicken, turkey and swine production.⁶ Roxarsone is the most common arsenic-containing compound.⁷ The Code of Federal Regulations (CFR) explains that when used alone, roxarsone is approved only for increased weight gain, improved feed efficiency, and improved pigmentation.⁸ Arsenic-containing feed additives, however, are generally compounds containing an arsenical such as roxarsone plus additional antibiotics and/or other antimicrobials.⁹ The European Union has never approved the use of arsenicals in animal feed, acknowledging the lack of science supporting health or safety standards for such use.¹⁰

⁵ Press Release, Congressman Steve Israel, *supra* n.4.

⁶ B.K. Anderson and T.N. Chamblee, *The Effect of Dietary 3-Nitro-4-Hydroxyphenylarsonic Acid (Roxarsone) on the Total Arsenic Level in Broiler Excreta and Broiler Litter*, 10 J. Applied Poultry Res. 323, 323–328 (2001).

⁷ Margaret Mellon et al., Union of Concerned Scientists, *Hogging it: Estimates of Antimicrobial Abuse in Livestock*_app. A, tbl. A-3 (2001), available at http://www.ucsusa.org/food_and_agriculture/science_and_impacts/impacts_industrial_agriculture/hogging-it-estimates-of.html (citing 21CFR558.62, 558.530).

⁸ 21 C.F.R. § 558.530. Roxarsone and arsanilic acid, when used alone, are only approved for weight gain, improved feed efficiency and improved pigmentation. *Id.* at § 558.62. However, FDA has approved the labeling of nitarsone and carbarsone alone for prevention and/or control of some diseases. *Id.* at 558.120; 558.369; 558.530. It is important to note, however, that such uses are much less likely than are uses of roxarsone and arsanilic acid, or uses of combination products that include antibiotics.

⁹ See generally Margaret Mellon et al., *supra* n. 7.

¹⁰ Comm. for Medicinal Products for Veterinary Use, European Medicines Agency, *Status of MRL Procedures: MRL Assessments in the Context of Council Regulations (EEC)*, No. 2377/90, EMEA/CVMP/765/99-Rev.23, available at <http://www.emea.europa.eu/pdfs/vet/mrls/076599en.pdf>.

Arsenic-containing compounds are most widely used in chicken production.¹¹ The vast majority of chickens will receive feed containing arsenic at some point in their lives. In 2004 and 2005, petitioner Institute for Agriculture and Trade Policy (IATP) tested for total arsenic in retail packages of raw chicken and in “fast food” chicken sandwiches and nuggets. Test results revealed detectable levels of arsenic in the majority of both supermarket and fast food chicken.¹² Relatively higher levels were observed in brands of chicken raised conventionally, with lower or non-detectable levels generally being found in certified organic and other “premium” brands where the use of arsenic-containing feed additives were either legally prohibited or claimed not to have been used. These results strongly suggest the use of arsenic-containing compounds in poultry feed leads to arsenic residues in U.S. marketed and eaten chicken.

The U.S. population is also regularly exposed to a cumulative burden of arsenic, such as that ingested in drinking water; the National Academies of Science estimates that 13 million Americans in 2001 were drinking water contaminated with arsenic at least at a 10 part per billion (ppb) level.¹³ FDA has recognized the human health hazard posed by arsenic in drinking water.¹⁴

¹¹ David Wallinga, Inst. for Agric. and Trade Policy, *Playing Chicken: Avoiding Arsenic in Your Meat* 11 (2006), available at <http://www.iatp.org/iatp/publications.cfm?accountID=421&refID=80529>.

¹² *Id.* at 21.

¹³ Subcomm. on Arsenic in Drinking Water et al., Nat'l Research Council, *Arsenic in Drinking Water* (National Academy Press 1999), available at http://www.nap.edu/catalog.php?record_id=6444; Subcomm. to Update the 1999 Arsenic in Drinking Water Report et al., Nat'l Research Council, *Arsenic in Drinking Water: 2001 Update* (National Academy Press 2001), available at http://www.nap.edu/catalog.php?record_id=10194; press release, Nat'l Academies of Sci., *New Evidence Confirms Cancer Risk from Arsenic in Drinking Water* (Sept. 11, 2001), available at <http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=10194>.

¹⁴ U.S. Food and Drug Admin., *Bottled Water: Arsenic Guidance for Industry Bottled Water: Arsenic Small Entity Compliance Guide* (Apr. 2009), available at <http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/ChemicalContaminantsandPesticides/ucm151384.htm>; U.S. Beverages: Bottled Water Final Rule, 70 Fed. Reg. 33,694 (June 9, 2005) (to be codified at 21 C.F.R. § 165.110(b)(4)(iii)), available at <http://www.fda.gov/Food/FoodSafety/Product-SpecificInformation/BottledWaterCarbonatedSoftDrinks/ucm077148.htm>; press release, U.S. Food and Drug Admin., *FDA Warns Again About Arsenic in Mineral Water* (Mar. 24, 2007), available at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108875.htm>.

Most of the arsenic ingested in poultry feed is subsequently excreted into poultry waste,¹⁵ where soil microbes (as is also true of microbes residing in gut microflora of humans and poultry) convert the arsenic to inorganic forms classified as human carcinogens.¹⁶ Since much poultry litter is applied as fertilizer to fields, this arsenic from feed is capable of further contaminating cropland or seeping into water tables.¹⁷ Approval of arsenic compounds in animal feed therefore exacerbates an already significant arsenic problem in America's food and drinking water supplies.¹⁸

Moreover, despite the now-discontinued use of arsenical pesticides, such as in treated wood products,¹⁹ in home products and on cropland,²⁰ families and schools continue to use decks, playground equipment and other structures made of arsenic-treated wood,²¹ and eat arsenic-contaminated foods grown on land previously treated with arsenical pesticides,²² thereby adding to their cumulative exposure to this potent poison.

Arsenic can cause additional human cancers even at the lower exposure levels currently found in contaminated food, water and the broader environment.²³ Arsenic exposure also contributes to other diseases, including heart disease, diabetes, and declines in intellectual

¹⁵ Joseph Louis Morrison, *Distribution of Arsenic from Poultry Litter in Broiler Chickens, Soil, and Crops*, J. 17 Agric. & Food Chem. 1288, 1288-90 (1969).

¹⁶ See *Infra* Statement of Grounds Section IV.B.

¹⁷ J.R. Garbarino et al., *Environmental Fate of Roxarsone in Poultry Litter. I. Degradation of Roxarsone during Composting*, 37 Env'tl. Sci. & Tech. 1509, 1509-14 (2003); D.W. Rutherford et al., *Environmental Fate of Roxarsone in Poultry Litter. Part II. Mobility of Arsenic in Soils Amended with Poultry Litter*, 37 Env'tl. Sci. & Tech. 1515, 1515-20 (2003).

¹⁸ See Organic Arsenicals; Product Cancellation Order and Amendments to Terminate Uses, 74 Fed.Reg. 50,187 Sept. 30, 2009).

¹⁹ Notice of Receipt of Requests to Cancel Certain Chromated Copper Arsenate (CCA) Wood Preservative Products and Amend to Terminate Certain Uses of CCA Products, 67 Fed. Reg. 8,244 (Feb. 22, 2002), available at <http://www.epa.gov/EPA-PEST/2002/February/Day-22/p4306.htm>.

²⁰ *Supra* n. 18.

²¹ V.G. Zatarian et al., U.S. Env'tl. Prot. Agency, *A Probabilistic Risk Assessment for Children Who Contact CCA-Treated Playsets and Decks* 6 (Feb. 2005) (2003), available at http://www.epa.gov/heads/sheds/CCA_all.pdf; press release, Env'tl. Working Group, *90 Percent of Children Face Elevated Cancer Risk* (Nov. 13, 2003), available at <http://www.ewg.org/node/8700>.

²² *Elevated Arsenic Levels Reported in Rice Grown in South Central States*, Science Daily (Mar. 5, 2007) available at <http://www.sciencedaily.com/releases/2007/03/070305092336.htm>.

²³ See Margaret Mellon et al., *supra*, at n.7.

function.²⁴ Additionally, new evidence suggests arsenic exposure inhibits the body's ability to respond to infectious agents, like the H1N1 virus.²⁵

Therefore, feeding arsenic to food animals further adds to an already significant human threat from arsenic exposure in our environment. Specifically, the use of arsenic in food animal production, and the likely ingestion of additional arsenic in chicken, is a needless and an unreasonably harmful addition to Americans' already health-impacting cumulative exposure to a carcinogen. Based on these facts, we respectfully request that FDA conduct the necessary evidentiary hearings and withdraw approval of roxarsone and other additional arsenical additives to animal feed.

²⁴ *Infra* n. 51; Subcomm. on Arsenic in Drinking Water et al., *supra* n. 13; Subcomm. to Update the 1999 Arsenic in Drinking Water Report et al., *supra* n. 13; Gail A. Wasserman et. al., *Water Arsenic Exposure and Children's Intellectual Function in Araihasar, Bangladesh*, 112 *Envtl. Health Persp.* 1329, 1329-33 (2004); S.Y. Tsai et al., *The Effects of Chronic Arsenic Exposure from Drinking Water on the Neurobehavioral Development in Adolescence*, 24 *Neurotoxicology* 747, 747-53 (2003).

²⁵ Courtney D. Kozul et al., *Low-dose Arsenic Compromises the Immune Response to Influenza an Infection in Vivo*, 117 *Envtl. Health Persp.* 1441, 1441-47 (2009).

STATEMENT OF GROUNDS

I. CURRENT USES: ARSENIC IN POULTRY FEED

Arsenical feed additives are FDA-approved for use in chicken, turkey and swine.²⁶ Most arsenical feed additives are used in poultry production; for example, according to the U.S. Food and Drug Administration's on-line "Green Book," there are 105 FDA-approved arsenic products for broiler chickens.²⁷ Of the 8.7 billion or so broiler chickens produced annually in the U.S., an estimated 70 percent are fed arsenic-containing compounds at some point in their lives. Most commonly this is an arsenical called roxarsone, but could also include arsanilic acid or nitarsone.²⁸

Unfortunately there are no public data to quantify the amount of arsenic compounds given to poultry.²⁹ However, the Union of Concerned Scientists (UCS) estimates nearly 2 million pounds of roxarsone alone are given annually to U.S. chickens, based on the 1998 production of 7.8 billion broilers.³⁰ Applying the UCS estimates to today's broiler production levels would lead to an estimate closer to 2.2 million pounds of roxarsone alone given to chickens annually.

A single company, Alpharma, accounts for the production of over half of all roxarsone-containing products.³¹ Alpharma's data provide another basis for estimation of the amount of arsenicals being distributed to poultry. An estimated 70 percent of broiler chickens on starter rations and approximately 74 percent of those on grower rations in the United States are receiving roxarsone,³² while Alpharma has claimed that a U.S. broiler on roxarsone-containing

²⁶ Center for Veterinary Medicine, U.S. Food and Drug Administration, Green Book On-Line, *available at* <http://www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/UCM042847>.

²⁷ *Id.*

²⁸ See 21 C.F.R. §558.35-.680 (2009); H.D. Chapman, Z.B. Johnson, *Use of Antibiotics and Roxarsone in Broiler Chickens in the USA: Analysis for the Years 1995 to 2000*, 81 Poultry Sci. 356, 356-64 (2002).

²⁹ See Margaret Mellon et al., *supra*, at n.7.

³⁰ David Wallinga, *supra* n. 11, at 13 fig. C.

³¹ David Wallinga, *supra* n. 11, at 13 tbl. 5.

³² H.D. Chapman, *supra* n. 28.

feed will get 3.5 mg of roxarsone daily for its six-week lifespan (minus a 5-day withdrawal period).³³ Therefore, if 70 percent of all broilers are on arsenical feed additives, then around 1.7 million pounds of roxarsone is fed to broilers annually. Hence, industry and other estimates roughly agree that at least 1.7 to 2.2 million pounds of roxarsone is given to American broiler chickens each year.

II. IATP TEST RESULTS: THE PREVALENCE OF ARSENIC IN RETAIL CHICKEN

From December 2004 to January 2005, a commercial laboratory tested for total arsenic in 151 different packages of retail chicken meat collected by IATP. IATP undertook this testing in large part because, although FDA approves the use of roxarsone and other arsenicals in chicken feed, and sets tolerances or legal levels for total arsenic in food, FDA does not monitor the usage of roxarsone or other arsenicals in animal feed. For enforcement of the tolerances, FDA relies upon USDA's Food Safety Inspection Service (FSIS). While the FSIS subsequently has begun some testing of more commonly consumed poultry and pork products, prior to the IATP testing it had not. In 2001, for example, the FSIS analyzed just 1,207 of the more than 8 billion or so young chickens produced for total arsenic, and then only chicken livers and not the muscle meat that is mostly consumed.³⁴

In testing retail raw chicken products, IATP included thighs, breasts and livers purchased under both "conventional" and "premium" labels. IATP tested chicken from five of the top 25 broiler producers nationally, several premium brands, and a single kosher/halal brand. IATP's

³³ Georges-Marie Momplaisir et al., Nat'l Exposure Research Lab. – Las Vegas, U.S. Env'tl. Prot. Agency,, *Arsenic Speciation Methods for Studying the Environmental Fate of Organoarsenic Animal-Feed Additives* (TIM No. 01-11) (2001), available at <http://www.epa.gov/esd/chemistry/labmonitor/arsenic.pdf>.

³⁴ U.S. Dept. of Ag., 2001 FSIS National Residue Program Data, at tbl. 3.3 available at http://www.fsis.usda.gov/OPHS/red_book_2001/2001_Residue_Program_Data_Sections1-7.pdf; Tamar Lasky et al., *Mean Total Arsenic Concentrations in Chicken 1989-2000 and Estimated Exposures for Consumers of Chicken*, 112 Env'tl. Heath Persp. 18, 18-21 (2004).

results indicated that arsenic is common in uncooked chicken products from supermarkets, being detected in 55 percent of tested products.³⁵

IATP also tested 90 samples of cooked “fast food” chicken products, purchased from restaurant chains focused on fried chicken, as well as from sandwich and burger outlets that offer chicken sandwiches, strips and nuggets. These tests revealed detectable levels of total arsenic in 100 percent of the tested samples.³⁶ The IATP testing did not attempt to “speciate” or distinguish organic or inorganic forms of arsenic in the total arsenic detected.³⁷

III. AMERICANS INCREASED CONSUMPTION AND THEREBY EXPOSURE TO ARSENIC IN FOOD ANIMALS

Americans are a “nation of meat eaters” whose meat consumption is at a record high.³⁸ With this increased consumption comes increased exposure to arsenic. Chicken, pork and turkey represent the first, third and fourth most heavily consumed foods from animals in America. While chicken is at the top of the list and by far poses the most significant risk for exposure, Americans’ turkey consumption also continues to rise. Statistics from the National Turkey Federation indicate that in 2008, Americans ate an average of 17.6 pounds of turkey, an increase of 108 percent since 1970.³⁹ Since 1970, the percentage of all turkey consumed for the holidays

³⁵ David Wallinga, *supra* n. 11, at 21-22.

³⁶ *Id.* at 23-24.

³⁷ It is true the levels of arsenic in chicken detected by the IATP methodology are lower than what the FDA would consider a tolerance violation. The purpose of the FDA’s more recent testing has been only to determine whether or not there is a tolerance violation. For the purpose of this petition, however, the IATP testing suggests that arsenic is prevalent in chicken meat, and that it contributes to cumulative exposures from this and other sources.

³⁸ USDA, AGRICULTURE FACT BOOK ch. 2, (2002) *available at* www.usda.gov/factbook/chapter2.htm.

³⁹ The National Turkey Federation, *The Perfect Protein* (2009) *available at* <http://www.eatturkey.com/consumer/stats/stats.html>.

declined from 50 percent to 29 percent.⁴⁰ Moreover, pork consumption remains constant; in 2008, Americans consumed an average of 49.5 pounds of pork.⁴¹

The routine presence of arsenic in food animals is most significant in light of Americans' increased consumption of chicken. From 1966 to 2000, annual chicken consumption rose 253 percent, from 32.1 to 81.2 pounds per person.⁴² Americans on average now eat 250 percent more chicken than they did 40 years ago. Some groups, however, are above average in their chicken consumption, and accordingly in their arsenic exposure. USDA data indicate that African-Americans eat about 20 percent more chicken than does the U.S. population as a whole; similarly, due to their small size, toddlers eating chicken baby food may ingest chicken at substantially higher than average levels, on a weight-adjusted basis.

IV. HUMAN SAFETY: EXPOSURE TO ARSENIC AND THE HEALTH RELATED HARM

A. The Health Effects of Arsenic

Arsenic exists in various forms, both organic and inorganic. Inorganic arsenic is one of the few substances studied well enough in people to be considered a “known” cause of human cancer – as early as 1879, high rates of lung cancer in Saxony miners were attributed in part to inhaled arsenic. By 1992, the combination of evidence from Taiwan and elsewhere was sufficient to conclude that ingested inorganic arsenic, such as is found in contaminated drinking water or food, was likely to increase the incidence of several internal cancers.⁴³ The link to skin

⁴⁰ Id.

⁴¹ Id.

⁴² David A. Taylor, *Funky Chicken: Consumers Exposed to Arsenic in Poultry*, 112:1 *Envtl. Health Persp.* A50 (2004) (reviewing Tamar Lasky et al., *Mean Total Arsenic Concentrations in Chicken 1989-2000 and Estimated Exposures for Consumers of Chicken*, 112 *Envtl. Health Persp.* 18, 18-21 (2004)).

⁴³ Int'l Agency for Research on Cancer, World Health Organization, *Some Metals and Metalloid Compounds: Summary of Data Reported and Evaluation*, 23 IARC Monographs on the Evaluation of Carcinogenic Risks to

and lung cancer is particularly strong and longstanding, although arsenic may cause liver, bladder, kidney and colon cancers as well.⁴⁴

The National Academies of Science estimate that Americans who drink water contaminated with arsenic at a 10 part per billion (ppb) level—numbering 13 million in 2001—have a greater than 1-in-300 risk of developing cancer during their lifetime.⁴⁵ For those 13 million Americans, in particular, arsenic-specific cancer risks already are much higher than for the population as a whole, disregarding additional sources of arsenic exposure beyond drinking water.

In 2009, however, the European Food Safety Authority (EFSA) issued new warnings to children and some consumers about the risks of inorganic arsenic *in food*.⁴⁶ Based on new science on the health risks of arsenic exposure in food, the EFSA panel on contaminants in the food chain (CONTAM) recommended that dietary exposure to inorganic arsenic should be reduced. CONTAM noted that “since the provisional tolerable weekly intake of 15µg/kg b.w. was established by the Joint FAO/WHO Expert Committee on Food Additive (JECFA), new data has established that inorganic arsenic causes cancer of the lung and urinary tract in addition to skin, and that a range of adverse effects has been reported *at exposures lower than those reviewed by the JECFA*.”⁴⁷

Arsenic also is not poisonous to everyone to the same degree. Children, infants, and the human fetus are among those most vulnerable to arsenic’s toxic effects. This is due to differences

Humans, 39 (1980); Subcomm. on Arsenic in Drinking Water et al., *supra* n. 13; Subcomm. to Update the 1999 Arsenic in Drinking Water Report et al., *supra* n. 13.

⁴⁴ Agency for Toxic Substances and Disease Registry, Ctrs. for Disease Control and Prevention, *Case Studies in Environmental Medicine (CSEM): Arsenic Toxicity Physiologic Effects*, available at http://www.atsdr.cdc.gov/csem/arsenic/physiologic_effects.html#carcino (last accessed Nov. 18, 2009).

⁴⁵ Press Release, Nat’l Academies of Science, *supra* n. 14.

⁴⁶ European Food Safety Auth. Panel on Contaminants in the Food Chain, European Food Safety Auth., *Scientific Opinion on Arsenic in Food*, 7 EFSA Journal 1351, Summary at 2 (2009).

⁴⁷ *Id.*

in arsenic metabolism between an adult and those very early in life—arsenic and its organic metabolites easily pass the placenta, for example.⁴⁸ Carcinogens like arsenic are generally more potent in their early life exposures. Following its review of 23 peer-reviewed studies of cancer incidence over the past 50 years, for example, the Environmental Protection Agency (EPA) concluded infants up to age two are, on average, ten times more vulnerable to carcinogenic chemicals than adults, and for some cancer-causing agents are up to 65 times more vulnerable; children ages 2-15 are merely three times more vulnerable to carcinogens than adults, EPA found.⁴⁹

An increased risk of cancer is not the only adverse impact of arsenic. Arsenic affects nearly all organ systems because it targets ubiquitous enzyme reactions in cells.⁵⁰ Long-term exposure to arsenic can also cause hyperpigmented skin, skin nodules, vessel disease, and appears to heighten the risk of death from high blood pressure and heart disease. Those repeatedly exposed to arsenic also have an increased risk of diabetes.⁵¹

There has been little effort until recently to study the non-cancer effects of arsenic exposure on early child development. Nevertheless, some animal studies suggest that arsenic causes birth defects and some human studies link arsenic in drinking water to increases in miscarriage, stillbirth, and preterm birth.⁵² Among children drinking contaminated water, arsenic has been associated with worse intellectual function and other neurocognitive deficits.⁵³

⁴⁸ Subcomm. to Update the 1999 Arsenic in Drinking Water Report et al., *supra* n. 13; M. Nathaniel Mead, *Arsenic: In Search of an Antidote to a Global Poison*, 113:6 *Envtl. Health Persp.* A378, A378-86 (2005).

⁴⁹ Risk Assessment Forum Technical Panel, U.S. *Envtl. Prot. Agency, Supplemental Guidance for Assessing Cancer Susceptibility from Early-Life Exposure to Carcinogens (External Review Draft)*, EPA/630/R-03/003, (Feb. 28, 2003) available at <http://cfpub.epa.gov/ncea/cfm/recorddisplay.cfm?deid=55446>.

⁵⁰ *Supra* n. 43.

⁵¹ Subcomm. on Arsenic in Drinking Water et al., *supra* n. 13; Subcomm. to Update the 1999 Arsenic in Drinking Water Report et al., *supra* n. 13.

⁵² *Id.*

⁵³ Gail A. Wasserman et al., *supra* n. 24; S.Y. Tsai et al., *The Effects of Chronic Arsenic Exposure from Drinking Water on the Neurobehavioral Development in Adolescence*, 24 *Neurotoxicology* 747, 747-53 (2003).

Scientists continue to discover new health impacts not previously considered from arsenic exposure. For example, evidence now indicates arsenic is a potent disruptor of hormone function, altering the way in which hormones transmit information between cells at extremely low levels of exposure.⁵⁴ Recently, a delayed response in developing immunity to the H1N1 virus was attributed to arsenic exposure in drinking water.⁵⁵

B. Organic and Inorganic Arsenic

The National Research Council has found no evidence “that arsenic is an essential element in humans or that it is required for any essential biochemical process.”⁵⁶ Conventional wisdom used to be that ingesting *organic* arsenics, like those added to animal feed, carried fewer health concerns than ingesting the *inorganic* forms of arsenic, such as those often found in tap water. Very limited study of the toxicity of roxarsone, an organic form of arsenic, had once led to the presumption it was not all that toxic.

More recent science calls that presumption into question. Environmental bacteria, including those residing in chicken litter as well as in the bacterial “microflora” of the human or chicken gut, convert roxarsone into inorganic forms such as arsenate, As(V), and arsenite, As(III), classified as human carcinogens, and therefore potentially more toxic than the parent compound.⁵⁷ Further, a variety of studies in cells demonstrate that exposure to infinitesimally small (nanomolar to low micromolar) concentrations of arsenite stimulates a process of new

⁵⁴ M. Nathaniel Mead, *supra* n. 48; Ronald C. Kaltreider et. al., *Arsenic Alters the Function of the Glucocorticoid Receptor as a Transcription Factor*, 109 *Envtl. Health Persp.* 245, 245-51 (2001); Jack E. Bodwell et al., *Arsenic at Very Low Concentrations Alters Glucocorticoid Receptor (GR)-Mediated Gene Activation but not GR-Mediated Gene Repression: Complex Dose-Response Effects Are Closely Correlated with Levels of Activated GR and Require a Functional GR DNA Binding Domain*, 17 *Chem. Research in Toxicology* 1064 (2004).

⁵⁵ *Supra* n. 25.

⁵⁶ Subcomm. on Arsenic in Drinking Water et al., *supra* n. 13.

⁵⁷ A.J. Bednar et al., *Photodegradation of Roxarsone in Poultry Litter Leachates*, 302:1-3 *Sci. Total Env't.* 237, 237-245 (2002); J.R. Garbarino et al., *supra* n. 17; John F. Stolz et al., *Biotransformation of 3-Nitro-4-Hydroxybenzene Arsonic Acid and Release of Inorganic Arsenic by Clostridium Species*, 41 *Envtl. Sci. & Tech.* 818, 818-23 (2007).

blood vessel formation called angiogenesis, associated with vascular disease as well as the growth of new tumors.⁵⁸ In addition to enhancing tumor growth, increased angiogenesis would contribute to overall growth potential and increased tissue pigmentation—exactly the attributes sought in roxarsone’s use as a poultry feed additive. In contrast, and despite its use over 60 years, the direct effects of roxarsone on mammalian cells have not been greatly studied so as to ensure its safety. In one exception, human cells from vascular and lung tissue were studied following exposure to roxarsone.⁵⁹ The study found that like arsenite, As(III), roxarsone induces an increase in angiogenesis, but it does so more potently. Moreover, roxarsone acts via a mechanism that is distinct and independent of the one induced by As(III). In other words, roxarsone use and exposure could potentially promote angiogenesis—a key element of cancer tumor growth—via two independent processes, one via conversion to As(III), and another via a more direct mechanism.

Further, an earlier history of organic arsenical toxicity has been largely overlooked. Arsenicals were once used to treat human syphilis and parasitic infections, as I.V. trivalent arsenic⁶⁰ and as an oral organic arsenical,⁶¹ respectively. In both cases, arsenical encephalopathy, and even death, could result at then recommended dosage levels and even after exposure to a single dose. To our knowledge, potential long-term changes to the brain and nervous system from routine, chronic exposure to organic arsenic residues in meat has never been evaluated.

⁵⁸ Chandrashekhar D. Kamat et al., *Role of HIF Signaling on Tumorigenesis in Response to Chronic Low-dose Arsenic Administration*, 86 *Toxicological Sci.* 248, 248–57 (2005); Bing Liu B et al., *Opposing Effects of Arsenic Trioxide on Hepatocellular Carcinomas in Mice*, 97 *Cancer Sci.* 675, 675–81 (2006); Nicole V. Soucy et al., *Arsenic Stimulates Angiogenesis and Tumorigenesis in Vivo*, 76 *Toxicological Sci.* 271, 271–79 (2003); Nicole V. Soucy et al., *Neovascularization and Angiogenic Gene Expression Following Chronic Arsenic Exposure in Mice*, 5 *Cardiovascular Toxicology* 29, 29-41 (2005).

⁵⁹ Partha Basu et al., *Angiogenic Potential of 3-Nitro-4-Hydroxy Benzene Arsonic Acid (Roxarsone)*, 116 *Envtl. Health Persp.* 520, 520-23 (2008).

⁶⁰ Cole Monroe, et al., *Arsenical Encephalopathy Due to Use of Milibis*, 117 *Archive Internal Med.* 706, 706-711 (1966);

⁶¹ L. Krainer et al., *Arsenical Encephalopathy In Indian Troops*, 10 *J. Neurology Neurosurgery Psychiatry* 171, 171-182 (1947).

Moreover, the use of organic arsenicals in animal feed likely contributes to the epidemic spread of antimicrobial resistance currently threatening human as well as animal health. For resistance to form requires the presence of bacteria as well as the genetic elements that when acquired can make those bacteria resistant to one or multiple antibiotics. Animal production facilities, including hog manure and poultry litter, are rich bacterial sources. And the bacteria in poultry litter specifically have been found to contain large numbers of mobile genetic elements, or ‘integrons,’ that contribute to the spread and persistence of resistance genes.⁶² Multiple genes encoding for antibiotic resistance to different antibiotics are often grouped together on integrons that also contain genes coding for resistance to heavy metals, like arsenic. Bacteria with these integrons can survive exposure to any of the antibiotics or heavy metals to which they are resistant. Therefore, feeding heavy metals such as arsenicals routinely to poultry also can contribute to antibiotic resistance.⁶³

One final study bears mention. Xie et al. (2004) fed laboratory animals both organic and inorganic arsenic and looked at changes to the liver, an important organ for detoxification.⁶⁴ What the scientists found was surprising: arsenic accumulated in the liver regardless of whether it was organic or inorganic arsenic being fed to animals. In addition, *all forms of arsenic altered how liver cells interpret or “express” the genetic information* contained in those cells, even if the specific expression of these genes differed somewhat between organic and inorganic arsenic.

⁶² Jingrang Lu et al., *Evaluation of Broiler Litter With Reference to the Microbial Composition as Assessed by Using 16S rRNA and Functional Gene Markers*, 69 Applied & Env'tl. Microbiology 901, 901-08 (2003); Sobhan Nandi et al., *Gram-positive Bacteria Are a Major Reservoir of Class 1 Antibiotic Resistance Integrons in Poultry Litter*, 101 Proc. Nat'l Acad. Sci. 7118, 7118-22 (2004).

⁶³ A. Summers, *Genetic Linkage and Horizontal Gene Transfer, the Roots of the Antibiotic Multi-Resistance Problem* 17 Animal Biotechnology 125, 125-35 (2006).

⁶⁴ Yaxoing Xie et. al., *Biokinetics and Subchronic Toxic Effects of Oral Arsenite, Arsenate, Monomethylarsonic Acid, and Dimethylarsinic Acid in v-Ha-ras Transgenic (Tg.AC) Mice*, 112 Env'tl. Health Persp. 1255 (2004).

In other words, the science demonstrates there are numerous health-based reasons to avoid additional sources of arsenic exposure to our already significant “background” exposure, regardless of whether those additions are to organic or inorganic arsenic.

Earlier this year, EPA reached an agreement in principle with 19 registrants or companies manufacturing organic arsenical pesticides for use as home, garden or agricultural products. The outcome was that in September 2009, these companies withdrew their products from the market, including for example, Ortho Crabgrass Killer, Scotts Spot Grass and Weed Control and Acme Ready-To-Use Weed & Grass Killer, and EPA withdrew its FIFRA approval for these pesticides.⁶⁵ The docket for this action indicates the reason for cancellation is EPA’s concerns about such uses potentially contributing to additional exposure to inorganic arsenic in drinking water.⁶⁶

C. Americans Total Daily Exposure to Arsenic

While the FDA sets tolerances for arsenic in various individual foods, these limits do not take into consideration the effects of repeated and continued exposure to arsenic from multiple sources. For most Americans, chicken is not the only source of arsenic exposure. One of the most prevalent ways in which Americans have been exposed to arsenic is in drinking water. In 2001, the EPA lowered the 50 year old drinking water standards for arsenic.⁶⁷ The amount of arsenic legally allowed in tap water was dropped to 10 parts per billion—five-fold lower than the amount previously permitted.⁶⁸ The 13 million Americans (2001 estimates) drinking an average of 2 liters per day of water contaminated with arsenic at the EPA’s new standard of 10 ppb

⁶⁵ Supra n. 18.

⁶⁶ Letter from Richard Keigwin, Dir. of Special Review & Reregistration Div., U.S. Env’tl. Prot. Agency, to Pesticide Registrants, Re: Amendment to Organic Arsenicals RED (Apr. 22, 2009), *available at* <http://www.regulations.gov/search/Regs/home.html#documentDetail?R=090000648096e574>.

⁶⁷ National Primary Drinking Water Regulations; Arsenic and Clarifications to Compliance and New Source Contaminants Monitoring, 66 Fed.Reg. 6975 (Apr. 23, 2001).

⁶⁸ Id.

would be expected to ingest around 10 micrograms of inorganic arsenic per liter per day, or 20 micrograms in total.⁶⁹ Several years later, even with new drinking water standards in place, data suggests that over three million Americans are still exposed to illegal levels of arsenic in drinking water.⁷⁰

Arsenic was also used as a pesticide on “pressure-treated” lumber in the form of chromated copper arsenate (CCA), a pesticide mixture that is 22 percent arsenic by weight. The EPA ended the manufacture and sale of CCA-treated lumber in 2004.⁷¹ Generations of children who played on CCA-treated playground equipment and wood decks were exposed to potentially hazardous levels of arsenic. Disposal hazards from this longstanding use remain today.⁷²

Arsenical pesticides were used for decades on crops. Before they were banned, these pesticides contaminated many pesticide manufacturing sites as well as food-producing land. As a result, some Americans could be exposed today to significant dietary arsenic simply from ingesting rice with high arsenic levels.⁷³ In fact, the EFSA’s recent study found particularly high concentrations of arsenic in rice and rice based products.⁷⁴

Location is another factor. Neighbors of the many Superfund sites contaminated with the arsenic residues, including from mine tailings and arsenical pesticides, experience additional potential exposure. The arsenical pesticides sold until late 2009 in many home and garden

⁶⁹ Id.

⁷⁰ Charles Duhigg, *Millions in U.S. Drink Dirty Water, Records Show*, N.Y.TIMES, Dec. 8, 2009, at A-1.

⁷¹ U.S. Env’tl. Prot. Agency, Pesticides: Regulating Pesticides - Chromated Copper Arsenate (CCA) (Nov. 2008), available at <http://www.epa.gov/oppad001/reregistration/cca/>.

⁷² Jennar R. Jambeck et al., *Landfill Disposal of CCA-Treated Wood with Construction and Demolition (C&D) Debris: Arsenic, Chromium, and Copper Concentrations in Leachate*, 42 Env’tl. Sci. & Tech. 5740, 5740-5745 (2008).

⁷³ P.N. Williams, et al., *Market Basket Survey Shows Elevated Levels of Arsenic in South Central U.S. Processed Rice Compared to California: Consequences For Human Dietary Exposure*, 41 Env’tl. Sci. & Tech. 2178, 2178-83 (2007).

⁷⁴ Panel on Contaminants in the Food Chain, European Food Safety Authority, *Scientific Opinion on Arsenic in Food*, 7 EFSA J. 1351, summary at 2 (2009).

products, and doubtless remaining on many homeowners' shelves, are an additional source of exposure.

In short, while FDA sets standards or tolerances for allowable levels of arsenic in meat, such levels represent only a portion of the average American's total exposure to arsenic. Avoidable arsenic use in food animal production only adds to the so-far uncounted cumulative risk from our many exposures to arsenic, from both natural and man-made sources. Moreover, the exposure to additional arsenic in poultry and pork meat due to the use of arsenical feed additives is an easily preventable and potentially significant component of Americans' overall total exposure. A piecemeal approach to regulating Americans' exposure to arsenic has thus far been ineffective at measuring and setting standards for cumulative total exposure to a potent carcinogen that contributes to other non-cancer disease as well.

V. ENVIRONMENTAL IMPACT: ARSENIC WRECKING HAVOC ON OUR NATURAL ENVIRONMENT

FDA-approved arsenicals used in poultry production likely have indirect human and environmental impacts beyond the direct effects of ingesting arsenic residues in meat. The more than 8.7 billion U.S. broiler chickens raised each year generate 26 to 55 billion pounds of poultry litter or waste.⁷⁵ Of the approximately 2 million pounds of roxarsone fed to chickens each year, up to three-quarters will pass unchanged into poultry waste. As discussed in detail *supra*, roxarsone rapidly breaks down into other organic and inorganic forms of arsenic during waste

⁷⁵ Keeve E. Nachman et. al., *Arsenic: A Roadblock to Potential Animal Waste Management Solutions*, 113 *Envtl. Health Persp.* 1123, 1123-24 (2005).

storage and composting, after land application,⁷⁶ and in the water leaching from litter-applied fields.⁷⁷

Poultry litter disposal occurs in several different ways. Around 90 percent is applied to nearby fields and cropland as “fertilizer”,⁷⁸ which, according to various estimates, may disperse a half million to 2.6 million pounds of roxarsone and its degradation products into the environment annually.⁷⁹ Poultry litter containing arsenic is also fed to beef cattle. In January 2004, the FDA proposed banning the practice; however, the agency reversed course in October 2005 and decided to continue allowing it after all.⁸⁰ A relatively new practice has developed of converting poultry litter into fertilizer pellets to be sold for commercial use on crops, for home landscaping, gardening and on golf courses. This practice opens up entirely new avenues of arsenic exposure. Arsenic levels in these pellets are reportedly similar to those found in unprocessed poultry waste.⁸¹

The rising volume of poultry waste, as well as its geographic concentration, means that larger broiler chicken and other poultry production facilities now generate far more waste than can easily be disposed of through land application. In late 2002, Minnesota permitted the first

⁷⁶ J.R. Garbarino et al., *supra* n. 17; Kris Christen, *Chickens, Manure and Arsenic*, 35 *Envtl. Sci. & Tech.* 184A, 184A-85A (2001); B.P. Jackson et al., *Trace Element Speciation in Poultry Litter*, 32 *J. Env'tl. Quality* 535, 535-40 (2003).

⁷⁷ Yuji Arai et al., *Arsenic Speciation and Reactivity in Poultry Litter*, 37 *Env'tl. Sci. & Tech.* 4083, 4083-90 (2003); L. Elizabeth Williams et. al., *Adsorption and Transport of Arsenic (V) in Experimental Subsurface Systems*, 32 *J. Env'tl. Quality* 841, 841-50 (2003); D.W. Rutherford et al., *supra* n. 17.

⁷⁸ Miguel L. Cabrera & J. Thomas Sims, *Beneficial Use of Poultry By-Products: Challenges and Opportunities, in Land Application of Agricultural, Industrial, and Municipal By-Products* (James F. Power & Warren A. Dick eds., Soil Science Society of America 2000) (2000); D.W. Rutherford et al., *supra* n. 17; R.L. Wershaw et al., *Roxarsone in Natural Water Systems*, available at <http://water.usgs.gov/owq/AFO/proceedings/afo/pdf/Wershaw.pdf>.

⁷⁹ Miguel L. Cabrera & J. Thomas Sims, *Beneficial Use of Poultry By-Products: Challenges and Opportunities, in Land Application of Agricultural, Industrial, and Municipal By-Products* (James F. Power & Warren A. Dick eds., Soil Science Society of America 2000) (2000); D.W. Rutherford et al., *Environmental Fate of Roxarsone in Poultry Litter. Part II. Mobility of Arsenic in Soils Amended with Poultry Litter*, 37 *Env'tl. Sci. & Tech.* 1515, 1515-20 (2003); R.L. Wershaw et al., *supra* n. 78.

⁸⁰ Press Release, U.S. Food & Drug Admin., Expanded “Mad Cow” Safeguards Announced to Strengthen Existing Firewalls against BSE Transmission (Jan. 26, 2004), available at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2004/ucm108230.htm>.

⁸¹ *Supra* n. 75.

U.S. incinerator for the purpose of burning poultry litter for electricity generation.⁸² This questionable practice will contribute to air pollution from toxics and heavy metals such as arsenic contained in the waste. Neither pelletization nor incineration can destroy or detoxify arsenic; both would further disperse it into the human environment.⁸³

Because arsenic is an element, it neither degrades nor disappears. Therefore, the disposal of arsenic compounds only redistributes arsenic in a different form that can lead to soil and water contamination. It is estimated that 70-90 percent of arsenic in poultry litter becomes water soluble, meaning it can readily migrate through soils and into underlying groundwater.⁸⁴ Routine arsenical use in animal feed likely adds to the already significant public health burden from arsenic-contaminated drinking water supplies.⁸⁵

⁸² Minn. Pollution Control Agency, Air Emission Permit 15100038-001, Issued to Fibrominn LLC (Oct. 23, 2002), available at <http://www.pca.state.mn.us/air/permits/issued/15100038-001-aqpermit.pdf>

⁸³ Supra n. 75.

⁸⁴ B.P. Jackson et al., supra n. 76; J.R. Garbarino et al., supra n. 17.

⁸⁵ Supra n. 75; Yuji Arai et al., supra n. 77.

STATEMENT OF LEGAL GROUNDS

I. THE NEW ANIMAL DRUGS ROXARSONE, ARSANILIC ACID, NITARSONE AND CARBARSONE ARE NOT SAFE FOR CONSUMPTION AND MUST BE WITHDRAWN FROM THE MARKET.

Arsenic-containing compounds fed to poultry and other farm animals create an unnecessary burden on human health. These compounds form residues in the edible portions of animals grown for food and also collect in the animal manure and litter, which is then recycled into the food system or left to burden the environment as the compounds leach from the manure into surface water and groundwater. These arsenic-containing compounds are classified as New Animal Drugs by the FDA. FDA must withdraw new animal drugs that are no longer considered safe. New science about organic arsenicals indicates that these arsenic-containing compounds approved long ago have not been shown to be safe for use in food animal production. The U.S. population is already burdened with many sources of arsenic. The additional burden presented by arsenic-containing compounds in food animals is a risk not outweighed by the purported benefits of their use. For these and other reasons, FDA must immediately initiate proceedings to re-evaluate the safety of these arsenic-containing compounds and upon conclusion of these proceedings, withdraw the approvals of all arsenic-containing compounds.

A. Although Not New or Novel, Roxarsone and Other Arsenicals Are New Animal Drugs Approved by FDA for Use in Animal Feed.

A “new animal drug” is defined as “*any* drug intended for use for animals other than man, including any drug intended for use in animal feed...”⁸⁶ Roxarsone and other arsenic-

⁸⁶ 21 C.F.R. § 510.3(g) (2009), emphasis added.

containing compounds are animal drugs administered to food animals in animal feed.⁸⁷ FDA approved these arsenic-containing compounds as a “*new animal drug[s]*” for use in growing chickens, turkey and swine for the following purposes:

- Weight gain
- Improved feed efficiency
- Improved pigmentation
- “Control of Infectious Synovitis caused by *Mycoplasma synoviae* susceptible to chlortetracycline.”
- “Control of chronic respiratory disease (CRD) and air sac infection caused by *M. gallisepticum* and *Escherichia coli* susceptible to chlortetracycline.”
- “Reduction of mortality *due to E. coli* infections susceptible to chlortetracycline.”
- “As an aid for the prevention of blackhead.”⁸⁸

Although the term “*new animal drug*” implies that the drug must be novel to the market, such an assumption is actually misleading. Roxarsone, for instance, was first approved by the FDA in the mid-1940s. Since the 1940s, FDA has approved 105 arsenic-containing compounds for chicken alone. New evidence indicates these new animal drugs are not safe and should be withdrawn from the market.

B. FDA Must Withdraw the Approval of Roxarsone and Other Arsenic-Containing Feed Additive Compounds Because These New Animal Drugs Are Unsafe.

The FDA must withdraw the approval of a previously approved NADA when that drug is found to be unsafe.⁸⁹ Under FFDCFA §360(b), the Secretary shall, after due notice and

⁸⁷ 21 C.F.R. §§ 558.62; 558.120; 558.369; 558.530.

⁸⁸ Id.

⁸⁹ See 21 U.S.C. § 360b(e)(1).

opportunity for hearing to the applicant, issue an order withdrawing approval of a new animal drug if the Secretary finds:

- A) “[E]xperience or scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved or the condition of use authorized under subsection (a)(4)(A);”⁹⁰
- B) New evidence, tests, or methods developed since approval of the application show that the drug is not safe for use “under the conditions of use upon the basis of which the application was approved...; or”⁹¹
- C) New information, combined with the evidence available at the time the application was approved show a “lack of substantial evidence that such drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof.”⁹²

The above statutory language as well as Court decisions interpreting and applying it illustrate that this is mandatory duty. In Rhone-Poulenc, Inc. v. FDA, for example, the court held that the Commissioner must withdraw her approval when new evidence shows an animal drug to be unsafe.⁹³

When determining whether a new animal drug (or category of new animal drugs, as is the case here) must be withdrawn, two issues are considered: whether there is a reasonable basis from which serious questions about the safety of the new animal drug may be inferred; and, whether the use of the new animal drug under the approved conditions is shown to be safe.⁹⁴ Once withdrawal procedures are initiated, the Center for Veterinary Medicine has the “initial burden of producing new evidence that raises serious questions about the ultimate safety” of the

⁹⁰ 21 U.S.C. § 360b(e)(1)(A) (2009).

⁹¹ Id. at (e)(1)(B).

⁹² Id. at (e)(1)(C).

⁹³ Rhone-Poulenc, Inc. v. FDA, 636 F.2d 750, 752-53 (D.C. Cir. 1980) (upholding FDA’s order withdrawing the new animal drug approval for the use of diethylstilbestrol (DES)).

⁹⁴ Ctr. for Veterinary Med., Proposal to Withdraw Approval of the New Animal Drug Application for Enrofloxacin for Poultry, Docket No. 00N-1571, at 2 (Mar. 16, 2004) (Initial Decision).

new animal drug.⁹⁵ When this threshold burden is met, the manufacturer is required to demonstrate the safety and efficacy of the drug.⁹⁶

1. Serious questions exist about the safety of roxarsone and other arsenic-containing compounds.

“‘Serious questions’ [about the safety of a new animal drug] can be raised where the evidence is not conclusive, but merely suggestive of an adverse effect.”⁹⁷ The scope of ‘new evidence’ is not limited to data developed after a NADA is approved but includes the re-evaluation or novel application of pre-existing data.⁹⁸

Since the original approval of roxarsone in the mid-1940s, there is ample new evidence to demonstrate that arsenic-containing compounds are no longer “safe for use.” IATP’s test results strongly indicate that the arsenic contained in roxarsone and other arsenic-containing compounds is detectable in chicken sold on the market.⁹⁹ At the time that roxarsone was first approved the organic form of arsenic contained in these compounds was believed to be less harmful than the inorganic form, which is a known hazard to human health. Evidence now shows that microbes including those residing in the human gut can release inorganic arsenic from roxarsone and other arsenic-containing compounds and therefore the latter must be considered to represent a human health hazard as does the former.¹⁰⁰

In the decades following roxarsone’s initial approval, new evidence has emerged of the extent to which arsenic exposure poses a risk to American health. Today it is widely accepted that exposure to inorganic arsenic leads to cancer, hyperpigmented skin, skin nodules, and vessel

⁹⁵ Id. at 5; See also Rhone-Poulenc, Inc., 636 F.2d at 752 (D.C. Cir. 1980).

⁹⁶ Id.

⁹⁷ Id.

⁹⁸ Id.

⁹⁹ David Wallinga, supra n. 11, at 7-8.

¹⁰⁰ John F. Stolz et al., supra n. 57.

disease.¹⁰¹ In one newly released study, it appears that the ability to develop an immunity to the H1N1 virus is hindered by exposure to arsenic.¹⁰² Arsenic use in animal feeds may spur the development of antibiotic resistant strains of bacteria posing risks to animal and human health.

Further, in September, 2009, EPA announced that 19 companies voluntarily withdrew (and EPA is subsequently canceling) pesticide registrations for organic arsenical pesticides, further evidencing the potential dangers of organic arsenic.¹⁰³ Due to “agency concerns about drinking water contamination and ecological risk,” EPA determined cancellation was necessary.¹⁰⁴ In support of this decision, EPA asserts that inorganic arsenic converts to organic arsenic in the soil and therefore presents concerns regarding groundwater contamination and drinking water exposure.¹⁰⁵ This and other new evidence discussed *supra* and in the accompanying footnotes and sources included in the administrative record of this petition raise serious questions about the safety of arsenic-containing compounds in animal feed additives.

2. The cumulative effect of human consumption of the arsenic-containing compounds present in food animals along with the various additional sources of arsenic in the environment must be considered.

In evaluating the safety of a new animal drug, the FDA shall consider, among other relevant factors: (A) the probable consumption of such drug and of any substance formed in or on food because of the use of such drug, and (B) the cumulative effect on man or animal of such drug, taking into account any chemically or pharmacologically related substance.¹⁰⁶ IATP test results indicate that Americans consume arsenical feed additives when they eat chicken. The

¹⁰¹ Subcomm. on Arsenic in Drinking Water et al., *supra* n. 13; Subcomm. to Update the 1999 Arsenic in Drinking Water Report et al., *supra* n. 13.

¹⁰² *Supra* n. 25.

¹⁰³ *Supra* n. 18.

¹⁰⁴ Letter from Richard Keigwin, *supra* n. 66.

¹⁰⁵ *Id.*

¹⁰⁶ 21 U.S.C. § 360b(d)(2) (2009).

same is likely true for turkey and swine. Arsenic is also present in rice, seaweed, other food products, drinking water, treated wood and elsewhere in the environment.

Arsenic-containing compounds intentionally added to animal feed add to the already significant cumulative effects of arsenic on the U.S. population. Despite increased proof of the risks posed by exposure to arsenic, the average Americans cumulative exposure to arsenic has greatly increased in the years since roxarsone's approval. EPA has taken steps to reduce the public's exposure to arsenic in drinking water,¹⁰⁷ and yet there is now abundant evidence that the average American is still exposed to dramatically higher levels of arsenic from multiple sources, than was true when roxarsone was first approved. This cumulative exposure to arsenic is neither measured nor regulated as a whole. Consequently, ingestion of arsenic that is directly linked to the use of arsenic-containing compounds in animal feed has thus far been permitted to continue, despite new evidence of the extreme health risks associated with exposure to both inorganic *and* organic arsenic. As discussed at length *supra*, this cumulative exposure creates serious health concerns. Due to these serious concerns, FDA must immediately take steps to withdraw all arsenic-containing compounds from use in food animal feed.

3. The purported benefits of roxarsone and other arsenic-containing compounds do not outweigh the risk of harm.

In considering whether an animal drug is safe within the meaning of FFDCA 512(e)(1)(b) the “typical issue for the FDA is not the absolute safety of a drug...the issue for the FDA is whether to allow sale of the drug, usually under specific restrictions. Resolution of this issue inevitably means calculating whether the benefits that the drug produces outweigh the costs of its

¹⁰⁷ 74 Fed. Reg. 50,187; letter from Richard Keigwin, *supra* n. 66.

restricted use.”¹⁰⁸ In other words, a product’s “therapeutic benefits must outweigh its risk of harm.”¹⁰⁹

Here, the therapeutic gain does not outweigh the risk of harm. Roxarsone and other arsenic-containing compounds provide questionable benefit and in any case are not necessary for large-scale food animal production. For instance, chicken from the world’s largest chicken producer, Tyson, contains little or no arsenic residue.¹¹⁰ And, while there is abundant large-scale food animal production in the European Union, it never approved arsenic for use in animal feeds, further indicating that U.S. arsenical use is excessive and avoidable.¹¹¹

Juxtaposed against arsenic’s well-known cancer-causing properties, new evidence of inorganic arsenic’s non-cancer effects on human health, the conversion of organic to inorganic arsenic and the cumulative exposure to arsenic in poultry, other foods, water and the environment, the questionable benefit of arsenic-containing compounds in food animal production presents unsupportable and unnecessary risks to human health.

C. Failure of FDA to Investigate New Evidence Indicating that Roxarsone and Other Arsenic-containing Compounds are Unsafe is Arbitrary and Capricious.

In making a factual inquiry concerning whether an agency decision was “arbitrary and capricious,” a reviewing court must consider whether the decision was based on a reasoned

¹⁰⁸ Hess & Clark, Div. of Rhodia, Inc. v. FDA, 495 F.2d 975, 993-94 (D.C.Cir. 1974).

¹⁰⁹ FDA v. Brown & Williamson Tobacco Corp., 529 U.S. 120, 140 (2000) citing United States v. Rutherford, 442 U.S. 544, 555 (1979) (noting that “[t]he Commissioner generally considers a drug safe when the expected therapeutic gain justifies the risk entailed by its use.”)

¹¹⁰ David Wallinga, supra n. 11, at 7-8.

¹¹¹ Council Regulation 2377/90, 1990 O.J. (L 224) (EC) (repealed 2009 by Council Regulation 470/2009, 2009 O.J. (L 152) (EC))(Under Council Regulation 470/2009, Council Regulation 2377/90 remains in effect until new regulation classifying maximum residue limits of pharmacologically active substances come into force); European Medicines Agency, Summary Opinion of the Committee for Veterinary Medicinal Production the Establishment of Maximum Residue Limits: Roxarsone of 14 January 2004, *available at* <http://www.emea.europa.eu/pdfs/vet/mrls/mrlopinions/008304en.pdf>; David Wallinga, supra n. 11, at 7-8.

evaluation of the relevant factors and whether there has been a clear error of judgment.¹¹² An agency must cogently explain why it has made a particular decision and enable a court to conclude that it was the product of reasoned decision making.¹¹³

New evidence about arsenic-containing compounds in poultry feed is now before FDA. IATP's recent tests show that roxarsone and other arsenic-containing compounds in poultry feed lead to arsenic residue in chicken. Because new evidence indicates that the organic arsenic found in these compounds could be as harmful to human health as the inorganic form, roxarsone and other arsenic-containing compounds should be deemed "unsafe for use." Since they are unsafe for the use under which they were originally approved, FDA must initiate procedures to withdraw permission of arsenic-containing compounds in food animal feed. Failing to investigate this new scientific evidence and the cumulative impacts of arsenic in the environment concerning the possible human health risks of arsenic-based feed additives is contrary to the overarching intent of the FFDCA and would be a clear abdication of FDA's legal duty. Failing to initiate an evidentiary hearing on the safety of roxarsone and other arsenic-containing compounds can only be concluded as unreasoned decision making by the agency and an arbitrary and capricious agency action.

CONCLUSION

Americans are already exposed to health significant levels of arsenic from multiple sources. Eliminating the arsenic voluntarily added to animal feeds as an additional source of arsenic exposure is not only feasible, but a necessary preventative step to ensure the health of all Americans already exposed to arsenic in drinking water and other involuntary sources. For the

¹¹² Marsh v. Oregon Natural Resources Council, 490 U.S. 360, 378 (1989).

¹¹³ See Motor Vehicle Mfrs. Assn. v. State Farm Mut. Auto Ins. Co., 463 U.S. 29, 49 (1983).

aforementioned reasons, petitioners respectfully request FDA withdraw approval for the routine use of roxarsone, arsanilic acid, nitarsone, and carbarsone in food animal feeds.

In accordance with FDA regulation 21 C.F.R Part 10.30(e)(2), FDA must respond to the above petition within 180 days or risk arbitrarily and capriciously violating the regulation.

ENVIRONMENTAL IMPACT STATEMENT

The specific actions requested by Petitioners will not cause the release of any substance into the environment. They are categorically excluded from the requirement of environmental documentation under 21 C.F.R. § 25.33(g).

ECONOMIC IMPACT STATEMENT

The requested information is only required when requested by the Commissioner following the review of the petition, and therefore an economic impact statement is not provided at this time.

CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner that are unfavorable to the petition.

ENDORISING ORGANIZATIONS

The following organizations have endorsed this petition to FDA requesting that FDA immediately institute procedures to withdraw all new animal drug applications for the arsenical additives to food animal feed roxarsone, arsanilic acid, carbarsone and nitarsonsone:

Center for Biological Diversity
Center for Environmental Health
Ecology Center of Michigan
Food Animal Concerns Trust
Food and Water Watch
Health Care Without Harm
Institute for a Sustainable Future
National Sustainable Agriculture Coalition
Physicians for Social Responsibility - Oregon Chapter
Physicians for Social Responsibility - San Francisco Chapter