

DRAFT

Citizen Petition

to the U.S. Food and Drug Administration

Arkansas Legislative Task Force on Alpha-gal

November 7, 2016

Alpha-gal: Personal Impact

A 56-year-old Arkansas man awoke in the middle of the night suddenly covered in hives. Feeling lightheaded, he called for his wife and then lost consciousness. His blood pressure had dropped. An ambulance rushed him to the hospital. This wasn't the first time he'd suffered these sudden symptoms. Three years earlier the man suffered a similarly perplexing episode, with hives, swelling and fainting spells. He was taken off his blood pressure medication out of concern that it was causing the reaction. He began taking an antihistamine to stop the hives and other allergic symptoms, but stopped a few months later, leading to repeated bouts of hives, fainting spells and other problems.¹

On the night of his emergency room visit, the patient learned he'd had a dangerous allergic reaction to the pork he'd eaten earlier that evening. What's more, he learned his body's reaction to the pork actually started long before that evening with tick bites he received while outdoors. The man was diagnosed with an allergy to mammalian meat known as Alpha Gal syndrome, an allergy believed to be caused by the tick bites and then triggered by the consumption or ingestion of mammalian meat. The best treatment for stopping the mysterious attacks is steering clear of the mammalian products that cause them. But allergy sufferers, like this Arkansas man, must be alerted when products contain mammalian ingredients.

The members of the Arkansas Legislative Task Force on Alpha Gal submit this citizen petition to request the U.S. Food and Drug Administration support Congressional action requiring the labeling of all products intended for human ingestion or injection if they contain mammal meat or mammalian meat products, such as gelatin or glycerin.

About the Petition Signers

During Arkansas General Assembly's 2015 Regular Session, Representatives Julie Mayberry and Dwight Tosh introduced House Bill 1658 proposing the creation of the Task Force on Alpha-Gal. The full Legislature approved the measure, and in April

¹ Wagner, K.D., Bell, M.C., Pesek R.D., and Kennedy, J.L., Fifty-six-year-old man with anaphylaxis: A novel delayed food hypersensitivity reaction, The Journal of the Arkansas Medical Society, November 2015.

2015, it became Act 1247 of 2015.² The legislation noted the General Assembly's findings as follows:

- (1) Alpha-gal allergies are a reaction to galactose-alpha-1, 3-galactose, where the body is overloaded with immunoglobulin E antibodies on contact with the galactose carbohydrate;
- (2) Bites from the lone star tick (*Amblyomma americanum*), which transfer this carbohydrate to the victim, have been implicated in the development of this delayed allergic response which is triggered by the consumption of mammalian meat products;
- (3) Alpha-gal allergies most often occur in the central and southern states such as Arkansas, where the lone star tick is more prevalent;
- (4) A typical allergic reaction to Alpha-gal has a delayed onset, occurring four to eight (4-8) hours after the consumption of mammalian meat products, instead of the typical rapid onset with most food allergies;
- (5) Since the reaction to eating mammal meat is delayed by several hours, the proper diagnosis is often missed or misdiagnosed;
- (6) People who are affected by Alpha-gal have to be constantly vigilant about the ingredients they consume, because an allergic reaction can be severe and life-threatening; and
- (7) As doctors are not required to report the number of patients suffering with Alpha-gal, the true number of affected individuals is unknown.

Act 1247 noted that the Task Force's purpose is to "promote awareness and encourage efforts to treat Alpha-gal in the state," especially among emergency room medical professionals. The legislation called for a wide representation of individuals to serve on the Task Force. The following table provides information about the statutory representation of Task Force members, and the individuals selected to serve for each category.

² State of Arkansas, 90th General Assembly, Act 1247 of the 2015 Regular Session

Statutory Category of Representation	Task Force Member
Arkansas House of Representatives	Representative Julie Mayberry
Arkansas Senate	Senator Missy Irvin
Arkansas House of Representatives	Representative Dwight Tosh
Arkansas Insurance Department	Ms. Zane Chrisman
Arkansas Board of Nursing	Ms. Karen McCumpsey
Arkansas Hospitality Association	Ms. Montine McNulty
University of Arkansas, Division of Agriculture	Mr. Rick Cartwright
Arkansas Pharmacists Association	Mr. Mark Riley
Arkansas Agriculture Department	Mr. Wes Ward
Arkansas Department of Health	Dr. James Bledsoe
Arkansas Department of Health	Dr. Dirk Haselow
American College of Allergy Asthma and Immunology	Dr. Curtis Hedberg
University of Arkansas, Division of Agriculture	Dr. Kelly Loftin
University of Arkansas, Division of Agriculture	Dr. Michael Looper
American Academy of Allergy Asthma and Immunology	Dr. Tina Merritt
Arkansas Department of Health	Dr. Susan Weinstein
Arkansas Department of Health	Dr. Gary Wheeler

The Task Force has met four times since its creation and has heard presentations from the following experts at the forefront of this syndrome.

- Dr. Tina Merritt, Allergist-Immunologist, American Academy of Allergy, Asthma & Immunology
- Dr. Curtis Hedberg, Allergist-Immunologist, Hedberg Allergy and Asthma Center
- Dr. Scott Commins, Associate Professor, University of North Carolina School of Medicine
- Tina Moore, Founder, Alpha-gal Facebook Support Group
- Dr. Michelle Aldrich, Director, Industrial Bio-Test Laboratories
- Dr. James Bledsoe, Chief Physician Specialist, Arkansas Department of Health
- Ms. Montine McNulty, Director, Arkansas Hospitality Association
- Dr. Steven Gendel, Vice President, Food Allergen Division, IEH Laboratories and Consulting Group

- Dr. Kelly Loftin, Associate Professor/Extension Entomologist, Division of Agriculture, University of Arkansas, Fayetteville
- Howell Foster, Director, Poison Center and Drug Information

The topics reviewed included the history of Alpha-gal, common concerns regarding Alpha-gal, where the syndrome commonly occurs geographically, Arkansas's statewide response to Alpha-gal, an update on Alpha-gal research, best food safety practices for managing allergens, the clinical spectrum of mammalian meat product, the history of food allergen labeling in the United States, Arkansas Poison Control, and the methods of minimizing tick bite exposure.

Following a presentation on food allergen labeling in the United States, the Task Force voted unanimously to begin taking steps to advocate for labeling of products containing mammalian meat ingredients.

Introduction to Alpha-gal Allergy

Galactose-alpha-1, 3-galactose, more commonly known as Alpha-gal is a carbohydrate produced by mammals that causes an allergic reaction in some people. The allergy's identification is relatively new, with the first cases reported in a medical journal in 2007.³ People with the allergy have reported suffering from the allergic reaction after eating mammal meat or coming into contact with other mammalian products, such as milk, or products with mammalian ingredients, such as gelatin. Unlike other allergies, there is typically a delay—usually three to six hours—between exposure to the mammalian product and the allergic response, making the allergy sometimes difficult to identify and diagnose.⁴ The allergy is widely thought to be caused by a tick bite. People with this allergy typically report having a tick bite prior to developing the allergy, leading researchers to conclude that the tick bite is integral to the development of the allergy.⁵ Researchers believe the tick bite introduces the Alpha-gal into individuals. The Alpha-gal then causes the patient to develop antibodies that target

³ Van Nunen, S., Galactose-Alpha-1, 3-Galactose, Mammalian Meat and Anaphylaxis: A World-Wide Phenomenon, *Current Treatment Options in Allergy*, (2014). 1:262-277, DOI 10.1007/s40521-014-0022-0

⁴ Kar, I., Muglia, C., Monteleone, C. and Hermes-DeSantis, E., Alpha-Gal (Mammalian Meat): Implications for Pharmacists, *Pharmacy Times*, May 27, 2015.

⁵ Van Nunen, S., Galactose-Alpha-1, 3-Galactose, Mammalian Meat and Anaphylaxis: A World-Wide Phenomenon, *Current Treatment Options in Allergy*, (2014). 1:262-277, DOI 10.1007/s40521-014-0022-0

Alpha-gal when the person consumes or is injected with mammalian products. Alpha-gal allergic reactions range from hives (urticaria) to swelling under the skin (angioedema) to a drop in blood pressure causing a narrowing of the airways (anaphylaxis).⁶

Alpha-gal Incidence

Because the Alpha-gal allergy is so newly identified and documented, there are no official statistics collected or reported on its incidence. The first numbers appeared in 2007 when the Alpha-gal allergy was initially reported in the medical literature with 25 patients in Australia, 24 of whom had a tick bite history. In the years since, researchers have recorded other cases across the globe in Australia, France, Spain, Japan, Germany, Korea, Sweden, Switzerland, Central America and the United States⁷. As awareness of the condition increases among medical professionals, more cases are being documented each year. More than 100 cases were reported in the medical literature in 2013 alone. Although the numbers documented in the professional literature remain small, anecdotal clinical evidence suggests the actual incidence is many times larger. Allergists at the Vanderbilt Asthma, Sinus, and allergy Program in Nashville, Tennessee noted in 2016 that they are treating 160 patients with alpha-gal allergy.⁸ The University of North Carolina at Chapel Hill has treated 350 patients, and UNC researcher Dr. Scott Commins estimates there are more than 3,500 cases in the United States, with clinics diagnosing dozens of patients in Kentucky and Georgia, among other states.⁹ In Arkansas, 270 patients were diagnosed between January 2013 and September 2015. The patients were located in 33 of the state's 75 counties. Nearly 50 patients were diagnosed in each of two northwest Arkansas counties (Washington and

⁶ Kar, I., Muglia, C., Monteleone, C. and Hermes-DeSantis, E., Alpha-Gal (Mammalian Meat): Implications for Pharmacists, *Pharmacy Times*, May 27, 2015.

⁷ Van Nunen, S., Galactose-Alpha-1, 3-Galactose, Mammalian Meat and Anaphylaxis: A World-Wide Phenomenon, *Current Treatment Options in Allergy*, (2014). 1:262-277, DOI 10.1007/s40521-014-0022-0

⁸ Smith, T., Vanderbilt Asthma, Sinus, Allergy Program sees uptick in alpha-gal syndrome, March 31, 2016, Retrieved at <http://news.vanderbilt.edu/2016/03/asthma-sinus-allergy-alpha-gal-syndrome/>

⁹ Carroll, L., Tick Bite Linked to Rise in Red Meat Allergies. Why Now?, NBC News, April 20, 2016, Retrieved at <https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&cad=rja&uact=8&ved=0ahUKEwjyoNqv8dfMAhVU1WMKHedpAYwQFggcMAA&url=http%3A%2F%2Fwww.nbcnews.com%2Fhealth%2Fallergies%2Ftick-bite-linked-rise-red-meat-allergies-why-now-n559346&usq=AFQjCNGvEGDmftD4Aqxs9vTXQVqaYsKaJg&sig2=ezVziSwjse7WwoC2Mwu9Sw&bvm=bv.122129774,d.amc>

Benton).¹⁰ So apparently prevalent is this allergy that at least two of the state's 135 General Assembly members suffer from it.

Alpha-gal Patient Characteristics

Alpha-gal affects both men and women, and patients have been diagnosed at every age. In Arkansas, the allergy appears to be more frequently diagnosed in women, according to the results of Arkansas Alpha-gal lab tests conducted by Viracor IBT Laboratories. Between January 2013 and September 2015, 171 of the 270 documented Alpha-gal cases were females (63%) while 99 (37%) were males.

While adults have been diagnosed with Alpha-gal since 2007, the allergy was first officially documented in children in 2013. Kennedy et al. reported 45 patients under 18 with the characteristic antibody in their blood.¹¹ The 270 Arkansas Alpha-gal patients spanned every age group, from a baby under 1 year of age to two patients in their early 90s. The highest percentage of the Arkansas Alpha-gal patients fell between the ages of 40 and 60. Still, the spread in age among the Arkansas Alpha-gal patients was fairly even.

Age Group	% of Arkansas Patients
Under 20	19%
20 to Under 40	24%
40 to Under 60	34%
60 and Older	24%

Alpha-gal Geographic Distribution

While the Alpha-gal allergy has been linked to tick bites, researchers believe the allergy may be caused by one tick species in particular: the lone star tick (*Amblyomma americanum*).¹² Researchers have reached this conclusion, in part, because cases of Alpha-gal allergic reactions have occurred in southeastern parts of the United States and in other areas of the world where the lone star tick is common. According to the

¹⁰ Fields, VS and Haselow, DT. Unpublished Arkansas Department of Health data.

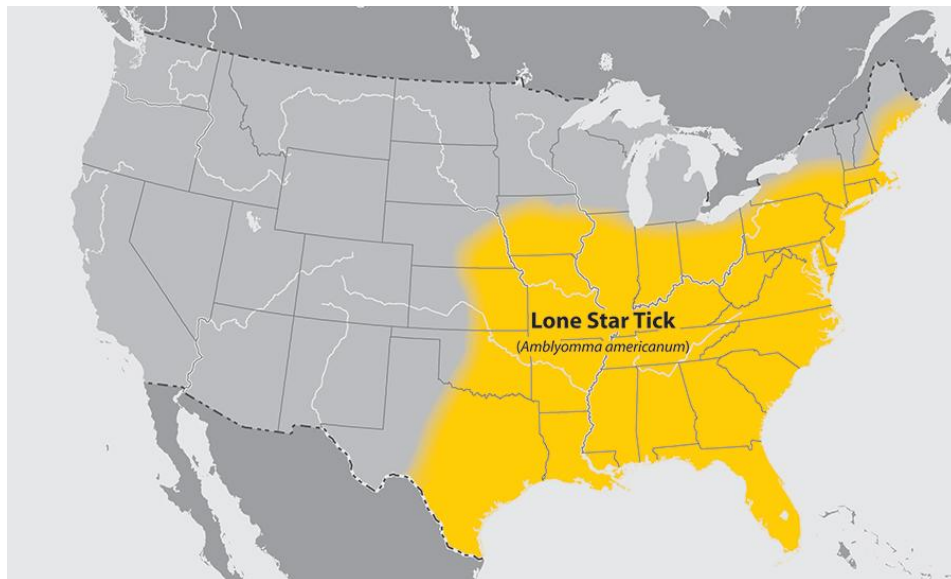
¹¹ Kennedy, J.L., Stallings, A.P., Platts-Mills, T.A.E., Oliveira, B.S., Workman, L., James, H.R., Tripathi, A., ... Commins, S.P., Galactose (2013). Galactose- α -1,3-galactose and Delayed Anaphylaxis, Angioedema, and Urticaria in Children. *Pediatrics*, 131, 5, e1545-e1552.

¹² Kar, I., Muglia, C., Monteleone, C. and Hermes-DeSantis, E., Alpha-Gal (Mammalian Meat): Implications for Pharmacists, *Pharmacy Times*, May 27, 2015.

U.S. Centers for Disease Control and Prevention, the lone star tick inhabits mostly eastern, southeastern and south-central states, but it has been found as far north as Maine and as far west as Texas and Oklahoma. “The distribution, range and abundance of the lone star tick have increased over the past 20-30 years,” according to the CDC,¹³ suggesting the potential for a broad and increasing incidence of Alpha-gal. (It should be noted that the CDC does not yet list Alpha-gal among its list of tickborne diseases: <http://www.cdc.gov/ticks/diseases/index.html>.)

Arkansas epidemiologists tracking the incidence of the allergy in this state have found a seasonal pattern with new cases spiking in the summer and fall months. When the 2013 and 2014 Arkansas cases are combined (the 2015 data did not include a full year), about 64% of the cases are identified in the summer and fall months. This appears to coincide with the seasonality of the lone star ticks, which are most prevalent in the summer months.¹⁴ Additionally the increase in the number of Alpha-gal cases has coincided with an increase in white-tailed deer, host animals for the lone star ticks.¹⁵

The following map shows the distribution of the lone star tick in the United States.



Source: Centers for Disease Control and Prevention, http://www.cdc.gov/ticks/maps/lone_star_tick.html

¹³ Centers for Disease Control and Prevention, Lone star tick a concern, but not for Lyme disease, retrieved May 17, 2016 at <http://www.cdc.gov/stari/disease/>.

¹⁴ Entomology & Nematology, University of Florida, Lone star tick, Retrieved May 17, 2016 at http://entnemdept.ufl.edu/creatures/urban/medical/lone_star_tick.htm

¹⁵ Van Nunen, S., Galactose-Alpha-1, 3-Galactose, Mammalian Meat and Anaphylaxis: A World-Wide Phenomenon, Current Treatment Options in Allergy, (2014). 1:262-277, DOI 10.1007/s40521-014-0022-0

The following map indicates that the incidence of the Alpha-gal allergy mirrors the distribution of the lone star tick. The large stars represent states with at least 25 cases as of 2011. The smaller stars indicate state where cases numbered between five and 24, and the dots indicate single cases.



Source: Commins SP, James HR, Kelly LA...Platts-Mills TA. The relevance of tick bites to the production of IgE ab to the mammalian oligosaccharide galactose- α -1,3-galactose. *J Allergy Clin Immunol.*, May, 2011, 127(5): 1286-1293.e6, retrieved at <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3085643/>

Severity of Alpha-gal

Though Alpha-gal syndrome is an allergy like those suffered by millions of Americans, its effects can be disruptive, dangerous and even fatal. As mentioned previously, Alpha-gal can cause an allergic patient to develop hives, rashes, itching and swelling of the hands, tongue and lips. One patient described the swelling in her hands as being as painful as being bitten by fire ants.¹⁶ In more severe cases, it can cause light-headedness, loss of consciousness and anaphylaxis. Many people with this allergy wind up in the emergency room, baffled and terrified by their worsening symptoms. In one study of pediatric patients, five of the 51 patients studied visited the emergency

¹⁶ Boerner, C., Red meat allergies likely result of lone star tick, Vanderbilt University Medical Center, Retrieved May 13, 2016 at <http://news.vanderbilt.edu/2014/02/red-meat-allergies-likely-result-of-lone-star-tick/>

room at least four times before being diagnosed with the allergy.¹⁷ A total of 45% of the children in that study used the emergency room at least once, and 8% of the patients were admitted to the hospital. In addition to being frightening and uncomfortable, the allergic reaction can be deadly. The research literature has documented at least one death in France due to Alpha-gal.¹⁸ Closer to home, Northwest Arkansas allergist Dr. Tina Merritt documented the death of a patient in 2006 after taking a medication that contained Alpha-gal.¹⁹

Avoiding Alpha-gal

Doctors advise that the most effective treatment for patients with Alpha-gal is to avoid exposure to products containing Alpha-gal. Patients should avoid eating pork, beef and other mammalian meat. Some patients have even reported having to avoid foods cooked in pans previously used to cooked pork or beef. Dairy products, such as cheese and milk may be tolerated by some with the allergy, but many sufferers cannot consume these products. Once patients know they have the allergy, meat and milk can be avoided relatively easily without special labeling.

That said, meat products and byproducts are contained in many foods and medications that are not so easily identified, such as canned vegetables flavored with meat. Research has found a connection between the Alpha-gal allergy and the gelatin that is often used to coat medications, including some antihistamines.²⁰ Patients who take gelatin-coated antihistamines to calm an allergic attack may inadvertently contribute to the problem.

The Alpha-gal health risk of medications isn't limited to pills with a gelatin coating. In 2008, oncology researchers documented a "hypersensitivity reaction" in 25 of 76 patients treated with the cancer drug cetuximab, a drug created from mouse cells. Oncologists noticed that a high number of patients taking the drug, which is

¹⁷ Kennedy, J.L., Stallings, A.P., Platts-Mills, T.A.E., Oliveira, B.S., Workman, L., James, H.R., Tripathi, A., ... Commins, S.P., Galactose (2013). Galactose- α -1,3-galactose and Delayed Anaphylaxis, Angioedema, and Urticaria in Children. *Pediatrics*, 131, 5, e1545-e1552.

¹⁸ Commins, S.P., Delayed Anaphylaxis to Red Meat in Patients with IgE Specific for Galactose alpha-1,3-Galactose (alpha-gal), *Current Allergy Asthma Report*, February 2013, 13(1): 72-77. Doi: 10.1007/s11882-012-0315-y

¹⁹ Merritt, T., IgE to Galactose 1,3- α -galactose in Arkansas presentation.

²⁰ Mullins, R.J., The relationship between red meat allergy and sensitization to gelatin and galactose-alpha-1,3-galactose (2012). *Journal of Allergy Clinical Immunology*, 129(5):1334-1342.e1. doi: 10.1016/j.jaci.2012.02.038.

administered through infusion into patients' veins, experienced severe hypersensitivity reactions within minutes of receiving the drug. When the researchers tested the patients' blood, they found 17 of those 25 patients had Alpha-gal antibodies, and the incidence of hypersensitivity was higher in the same southeastern states—Tennessee, Arkansas, and North Carolina—where the Alpha-gal allergy is most prevalent in this country.²¹ To address the problem with this therapy, researchers have developed a humanized version to reduce the allergic response some patients experienced from the mammalian version.

British researchers who published an analysis in the *British Medical Journal* noted that patients and even doctors are unaware that many medicines contain animal products. They advise better labeling of such medications. "Information about animal derived products in medicines is difficult to obtain, unclear, inconsistently reported, and sometimes incorrect," they wrote. "Improvement in drug labeling...would help inform prescribers, dispensers, and patients,".²²

Though much of the concern about the Alpha-gal allergy has focused on meat and medications, patients can be exposed to the allergen in many other ways. Gelatin is an ingredient in many food products and household items. The following list demonstrates the wide variety of gelatin-containing products and their ubiquity in daily life.

- Candy, such as marshmallows
- Food thickeners
- Dips
- Glazes and icing
- Fat substitute in some products
- Sausage coatings
- Salami

²¹ Chung, C.H., Mirakhur, B., Chan, E., Le, Q., Berlin, J., Morse, M., ... Platts-Mills, T.A.E., Cetuximab-Induced Anaphylaxis and IgE Specific for Galactose- α -1,3-Galactose (2008). *The New England Journal of Medicine*, 358:1109-17.

²² Tatham, K.C. and Patel, K.P., Suitability of common drugs for patients who avoid animal products (2014). *British Medical Journal*, 348:g401, doi: 10.1136/bmj.g401.

- Tinned hams
- Used to clarify fruit juice and wine
- Shampoo
- Collagen implants
- Sutures
- Contact lenses
- Used as a binding agent in some tablets, capsules and suppositories²³

Some patients with the Alpha-gal allergy have sensitivity to some types of glycerin that are derived from animal fats. Glycerin is a food additive found in canned goods, candy, fondant, processed fruits, jams and energy bars. It is also used in medications, syrups, toothpaste, mouthwash, and tobacco, among many other products.²⁴

Action Requested

The Food Allergen and Consumer Protection Act defines the foods formally recognized as major food allergens and requires products that contain them to be appropriately labeled. The Act's purpose was to alert consumers to the presence of allergens in the foods they eat so they can avoid consuming harmful products. The members of the Arkansas legislative Task Force on Alpha-gal understand the list of foods subject to the Food Allergen and Consumer Protection Act is under Congress's authority, not the U.S. Food and Drug Administration's. However, Congress relies on the FDA's guidance in determining changes to the federal labeling law. We ask that the FDA review the literature on the Alpha-gal allergy and support the inclusion of mammalian meat products among the list of major food allergens. We also ask that the agency support the labeling of Alpha-gal containing medications, cosmetics and other products. We believe that conspicuous labeling of products containing mammalian meat products is the best way to arm Alpha-gal sufferers against potentially life-threatening illness.

²³ Mullins, R.J., The relationship between red meat allergy and sensitization to gelatin and galactose-alpha-1,3-galactose (2012). *Journal of Allergy Clinical Immunology*, 129(5):1334-1342.e1. doi: 10.1016/j.jaci.2012.02.038.

²⁴ Nutrients Review.com, Glycerin, Retrieved May 19, 2016 at <http://www.nutrientsreview.com/carbs/edible-glycerin.html>