



Background on GBCAs

GBCA stands for Gadolinium-Based Contrast Agent. As the name indicates, [Gadolinium \(Gd\)](#) is the primary component of the GBCA complex that is injected intravenously during contrast-enhanced Magnetic Resonance Imaging (MRI) and Magnetic Resonance Angiography (MRA) scans. Note that MRI and MRA can also be performed without the administration of a contrast agent.

To fully explain Gadolinium-based Contrast Agents would require a substantial amount of scientific information and we will not attempt to go into that here. Instead, we will provide a general overview of MRI and GBCAs along with details about the different agents. We will also provide information related to FDA approvals and subsequent FDA warnings after the connection was made between GBCAs and [NSF](#) (Nephrogenic Systemic Fibrosis), formerly known as NFD (Nephrogenic Fibrosing Dermopathy).

Basic Principles of MRI

Magnetic Resonance Imaging or MRI is a medical procedure that uses strong magnetic fields, radiofrequency (RF) waves, and a computer to produce cross-sectional images of organs and internal structures in the body. The magnetic field temporarily realigns atomic particles called protons that are present in most of the body's tissues. The applied radio waves cause these protons to produce signals that are picked up by a receiver within the MR scanner. With the help of a computer, very clear images of tissues are created as "slices" that can be viewed in any orientation.¹ Because the signal detected by an MRI machine varies depending on the water content and local magnetic properties of a particular area of the body, different tissues or substances can be distinguished from one another in the study images.² Most diseases manifest themselves by an increase in water content, so MRI is a sensitive test for the detection of disease. However, the exact nature of the pathology can be more difficult to ascertain.³

MRI provides excellent soft tissue contrast on unenhanced images, and because of that, it was initially speculated that there would be no need for a contrast agent. In the early 1980s, it became apparent that contrast enhancement could substantially improve the sensitivity and specificity of scans.⁴ However, some have indicated that the use of different pulse sequences might allow for a greater percentage of diagnoses to be made without administration of a contrast agent.⁵

According to Dr. Robert Brasch, whose lab did some of the experimental imaging with Gadolinium chelates in the early 1980s, there is virtually an infinite variety of pulse intervals (TR) and echo delay (TE) times, each TR-TE combination yielding a different intensity value (shade of grey) for the same tissues. He said it could take hours to gather all the different images from a patient.⁶ Contrast agents

help to alleviate that problem by selectively increasing the intensity of pathologic processes and thereby minimizing the need for additional imaging sequences which saves both time and money.⁶

Although many people refer to contrast agents as a “dye”, paramagnetic contrast agents are not observed directly on the images. The enhancement that is seen on the MR images is the result of their magnetic effects.⁶

Development of GBCAs

Scientific work related to the use of paramagnetic agents to change MR imaging tissue contrast had begun by the late 1970s.⁶ By definition, paramagnetic substances possess a permanent magnetic moment. These magnetic moments are randomly aligned in the absence of an applied magnetic field such as occurs during Magnetic Resonance imaging. Paramagnetic metals like Gadolinium shorten the T1 and T2 relaxation times of surrounding hydrogen nuclei.⁷ Depending on the concentration of paramagnetic agents, this relaxation effect causes higher intensity MR signal or contrast enhancement.⁶

Gadolinium (Gd^{3+}) has the strongest relaxation rate of all the paramagnetic cations (positively charged ions) in the atomic table. Its 7 unpaired electrons provide Gadolinium with strong paramagnetic properties.⁸ However, the free Gd^{3+} ion is toxic. Because of that, it must be chelated or bound to a ligand to form a stable complex before it can be used as a contrast agent.^{6,9,10} The chelator protects the tissues from interactions with Gd^{3+} ions and enables rapid renal clearance of the Gd^{3+} ions to minimize biotransformation or accumulation in the body.¹¹

Biochemical differences among GBCAs are determined by the chemical structure of the chelator. The chelator can be linear or macrocyclic, and ionic or nonionic.¹²

In 1984, Hanns-Joachim Weinmann and colleagues published their article titled “Characteristics of Gadolinium-DTPA Complex: A Potential NMR Contrast Agent” which described the first Gadolinium-based Contrast Agent.¹³ Later in 1984, Carr et al reported findings from the first clinical experience in patients.⁹ Gd-DTPA, better known as Magnevist, received FDA approval for clinical use in the U.S. in 1988.¹⁴

Different Structural Types of GBCAs

Currently, there are 9 GBCAs approved by the U.S. Food and Drug Administration (Table 1). There are 7 extracellular (ECF) agents and 2 specialty agents (Ablavar and Eovist). We will focus on the 7 ECF agents: Magnevist, Omniscan, OptiMARK, MultiHance, ProHance, Gadavist, and Dotarem.

An intravenously administered ECF rapidly equilibrates in the intravascular and interstitial (space between cells) fluid compartments; these are referred to collectively as the extracellular compartment.¹⁵ Tissues with leaky capillaries and large interstitial spaces (e.g., malignant tumors, inflammation, etc.) enhance in the arterial phase and nearly all tissues enhance to some degree in the equilibrium phase. Exceptions are brain and testicular tissues due to their impermeable capillaries to the extracellular agents. When this “blood-tissue barrier” is intact, there is no interstitial space distribution.¹² (See [Background on Gadolinium](#) for more information.)

GBCAs are unique among pharmaceuticals, being water proton relaxation catalysts whose effectiveness is characterized by a rate constant known as relaxivity.¹⁶ The agents can be divided into different structural types (linear, macrocyclic, ionic, nonionic) based on the chemistry of the chelating ligands

whose primary purpose is to protect the body from dissociation of the relatively toxic Gd^{3+} ion from the ligand.¹⁶

The most important thermodynamic criterion is the selectivity of the ligand for Gd^{3+} over other endogenous metal ions, particularly zinc (Zn^{2+}). Ligands that have similar thermodynamic stability constants for Zn^{2+} and Gd^{3+} form complexes which are very toxic, due to Gd^{3+} release as a result of transmetallation of the complex in vivo with Zn^{2+} .¹¹

The chelating ligands are either linear or macrocyclic. Linear chelates are flexible open chains which do not offer a strong binding to Gd^{3+} . In contrast, the macrocyclic chelates offer strong binding to Gd^{3+} by virtue of being preorganized rigid rings of almost optimal size to “cage” the Gadolinium ion.¹⁷ That results in more stable complexes which are less likely to dissociate.^{18,19} GBCAs can also be nonionic (electrically neutral with no net charge) or ionic (charged).^{18,20}

Linear GBCAs – Omniscan and OptiMARK are both linear nonionic agents and they have the lowest stability constants.^{19,20} This low stability is believed to be related to the higher prevalence of NSF cases associated with these GBCAs.²¹

Magnevist and MultiHance are linear ionic agents. Based on in vitro Zn^{2+} transmetallation data, Omniscan has lower stability and MultiHance has higher stability compared with Magnevist.²² However, based on higher-level, human ex vivo data, there is essentially no difference in the amounts of Gd^{3+} released among the ionic linear agents MultiHance and Magnevist when measured in native human serum at 37°C.^{19,23}

Macrocyclic GBCAs – Dotarem is a macrocyclic ionic GBCA. ProHance and Gadavist are macrocyclic nonionic agents. ProHance and Dotarem have the highest combined thermodynamic and kinetic stability, reflecting the greater energy and time required to remove the Gadolinium ion from the ring structure in which it is held.²⁰

The stability of the GBCA seems to be an important factor in the pathogenesis of NSF fibrosis. GBCAs of low stability are likely to undergo transmetallation and release free Gd ions that deposit in tissue and attract circulating fibrocytes to initiate the process of fibrosis.¹⁷

While macrocyclic GBCAs have been found to be more stable than the linear agents, they are not risk free. Animal studies have reported detection of Gadolinium from macrocyclic agents in bone and other tissues.^{15,24,25,26} A recent paper by Tweedle, Kanal, and Muller noted that Pietsch and colleagues used a sensitive in vivo animal model to derive elimination time-courses for Gadolinium in the skin of rats; 364 days later, a small amount of Gadolinium was still present in the skin of rats administered a macrocyclic agent.¹⁹ And most important, there are now cases of NSF associated with macrocyclic agents as well.^{27,28}

FDA Approvals and Warnings

In 1988, the FDA approved Magnevist,²⁹ the first commercially available Gadolinium-based Contrast Agent. In 1992, ProHance³⁰ was approved, followed by Omniscan³¹ in 1993, OptiMARK³² in 1999, MultiHance³³ in 2004, Gadavist³⁴ in 2011, and Dotarem³⁵ in 2013. In addition to these 7 extracellular (ECF) agents, the blood-pool agent Ablavar³⁶ and the liver imaging agent Eovist³⁷ were both approved in 2008. The links provided in the footnotes will take you to the product labeling for each agent as of September 2014.

Besides its trade name, each agent is known by different generic names as well. For instance, you will see Magnevist referred to as Gd-DTPA and gadopentetate dimeglumine. Table 1 shows the names associated with each FDA approved Gadolinium-based Contrast Agent as well as the agent's structure and approval date.

Table 1. FDA Approved Gadolinium-based Contrast Agents

Trade Name	Chemical Names	Structure	Type	Approved
Magnevist	Gd-DTPA (gadopentetate dimeglumine)	Linear ionic	Extracellular	1988
Omniscan	Gd-DTPA-BMA (gadodiamide)	Linear nonionic	Extracellular	1993
OptiMARK	Gd-DTPA-BMA (gadoversetamide)	Linear nonionic	Extracellular	1999
MultiHance	Gd-BOPTA (gadobenate dimeglumine)	Linear ionic	Extracellular	2004
Eovist/Primovist	Gd-EOB-DTPA (gadoxetate disodium)	Linear ionic	Liver	2008
Ablavar/Vasovist	(gadofosveset trisodium)	Linear ionic	Blood-pool	2008
ProHance	Gd-HP-DO3A (gadoteridol)	Macrocyclic nonionic	Extracellular	1992
Gdavist	Gd-BT-DO3A (gadobutrol)	Macrocyclic nonionic	Extracellular	2011
Dotarem	Gd-DOTA (gadoterate meglumine)	Macrocyclic ionic	Extracellular	2013

From 1988 when Magnevist was first approved until 2006 when the connection between NSF and Gadolinium-based Contrast Agents was first made, the medical community and the FDA believed that GBCAs did not pose any exceptional risk to patients. However, in 2006, everything began to change.

Although it wasn't known at the time, the first evidence of a problem with GBCAs began to appear in 1997 when dialysis patients presented clinically with skin changes and joint contractures that could not be explained. It was later determined that the problem went far beyond the patients' skin; it affected internal organs and tissues as well. Researchers went to work trying to find the cause of NSF. In 2006, doctors in Europe first confirmed the link to Gadolinium-based Contrast Agents.^{38,39} (See [Background on NSF](#) for details.)

On June 8, 2006, the FDA issued a Public Health Advisory about Gadolinium-containing Contrast Agents for Magnetic Imaging (MRI).⁴⁰ That same day the FDA issued an alert to healthcare professionals that was updated 12/2006 and 5/23/2007.⁴¹ Updates to the Public Health Advisory were issued on 12/22/2006 and 5/23/2007.⁴²

In its first Public Health Advisory, the FDA said that reports had identified a possible link between NSF/NFD in patients with kidney failure and exposure to Gadolinium-containing contrast agents used at high doses for a procedure called Magnetic Resonance Angiography (MRA). At that time none of the GBCAs had been FDA approved for MRA. The agents were being used "off-label" for the procedure

that is often performed with doses up to three times higher than the approved dose for MRI. (The blood-pool agent Ablavar received FDA approval for MRA in December of 2008.)

By the time the next Public Health Advisory was issued on 12/22/2006, the FDA said that NSF/NFD might occur in patients with “moderate to end-stage kidney disease” after they have had an MRI or MRA with a Gadolinium-based Contrast Agent.

On May 23, 2007, the FDA announced that it had asked manufacturers to include a new boxed warning on the product labeling of all Gadolinium-based Contrast Agents.⁴³ The requested warning was to state that “patients with severe kidney insufficiency who receive gadolinium-based agents are at risk for developing a debilitating, and a potentially fatal disease known as nephrogenic systemic fibrosis (NSF).” In addition, it would state that “patients just before or just after liver transplantation, or those with chronic liver disease, are also at risk for developing NSF if they are experiencing kidney insufficiency of any severity.”

In that same news release, the FDA noted that NSF had developed following single and multiple administrations of the GBCAs, and when a specific agent was identified in the reports, Omniscan was the most commonly reported agent, followed by Magnevist and OptiMARK.

On December 8, 2009, a Joint Meeting of the Cardiovascular and Renal Drugs and Drug Safety and Risk Management Advisory Committee met to review Gadolinium-Based Contrast Agents and Nephrogenic Systemic Fibrosis.⁴⁴ Presentations were made by the FDA, GBCA manufacturers, and guest speakers.⁴⁵ Dr. Shawn Cowper’s slide presentation, Nephrogenic Systemic Fibrosis – History, Diagnosis and The Registry,⁴⁶ contained photos and other information that is included in “Nephrogenic systemic fibrosis: Clinicopathological definition and workup recommendations” by Girardi et al.⁴⁷ Dr. Cowper is a dermatopathologist, an expert on NSF, and he maintains the NSF Registry.⁴⁸

On September 9, 2010, the FDA issued a second news release to announce that new warnings were required on the use of Gadolinium-based Contrast Agents and enhanced screening was recommended to detect kidney dysfunction.⁴⁹ Three of the GBCAs – Magnevist, Omniscan, and OptiMARK – will be described as “inappropriate for use among patients with acute kidney injury or chronic severe kidney disease”. All GBCA labels will emphasize the need to screen patients to detect these types of kidney dysfunction before administration.

The “boxed warning” is very important; however, patients are not given a copy of the product labeling so it is unlikely that any patient will ever see the warning before he or she signs the consent form prior to their contrast-enhanced MRI or MRA.

Where things stand today

After the implementation of the FDA’s screening and use guidelines for GBCAs, there have been far fewer new cases of NSF reported. However, we do not believe that all patients adversely affected by retained Gadolinium have been accounted for.

Since late 2012, we have been in contact with the FDA regarding our concerns about Gadolinium Toxicity caused by retained Gadolinium in patients with normal kidney function (meaning an eGFR>60). As of October 2014, the FDA has not issued any Public Health Advisory or warning regarding the use of GBCAs since 2010.

As you can see on the other pages of the Background Section, there are many reasons to think that all patients exposed to Gadolinium-based Contrast Agents are at risk of retaining at least some

Gadolinium regardless of their level of renal function at the time of their contrast-enhanced MRI or MRA. The published literature supports that statement with findings of Gadolinium in both study animals and humans with normal kidney function. (See the Background pages on [NSF](#), [Gadolinium](#), and [Risk Factors](#) for details.)

Our [Self-Study of Retained Gadolinium](#) and our [Symptom Survey Report and Retention Study Update](#) provide compelling evidence of Gadolinium retention in patients with no history of kidney disease. We believe our findings warrant further professional investigation into Gadolinium retention from GBCAs in all patient populations, including those with normal kidney function.

Update on FDA Actions since 2014

On July 27, 2015, the FDA issued its first Safety Announcement involving gadolinium retention in patients with normal renal function, specifically gadolinium retention in the brain. According to the Safety Announcement, *“After being administered, GBCAs are mostly eliminated from the body through the kidneys. However, trace amounts of gadolinium may stay in the body long-term”*. It also says, *“It is unknown whether these gadolinium deposits are harmful or can lead to adverse health effects”*. The statement indicated that the FDA, including its National Center for Toxicological Research (NCTR), will study this possible safety risk further.

While not calling for any changes to product labeling or use restrictions of any particular agents, at that time, the FDA said, *“To reduce the potential for gadolinium accumulation, health care professionals should consider limiting GBCA use to clinical circumstances in which the additional information provided by the contrast is necessary. Health care professionals are also urged to reassess the necessity of repetitive GBCA MRIs in established treatment protocols.”*

The FDA 7-27-2015 Safety Announcement can be accessed here:
<http://www.fda.gov/Drugs/DrugSafety/ucm455386.htm>

If you have unexplained symptoms that you believe were caused by retained Gadolinium from a contrast MRI or MRA, please report it to the FDA by filing a MedWatch Adverse Event Report. Call 1-800-FDA-1088 or report via the FDA website at
<http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm>

It is important that Adverse Event Reports related to Gadolinium-Based Contrast Agents are filed with the FDA or the full scope of Gadolinium-related health problems may never be brought to light.

Patients outside the U.S. should report to their country’s equivalent governing agency.

¹ Magnetic Resonance Imaging (MRI) Safety. (n.d.). Retrieved October 1, 2014, from
http://www.radiologyinfo.org/en/safety/index.cfm?pg=sfty_mr

² Health, C. for D. and R. (n.d.). Medical Imaging - MRI (Magnetic Resonance Imaging). Center for Devices and Radiological Health. Retrieved from <http://www.fda.gov/Radiation-EmittingProducts/RadiationEmittingProductsandProcedures/MedicalImaging/ucm200086.htm>

- ³ Berger, A. (2002). Magnetic resonance imaging. *BMJ (Clinical research ed.)*, 324(7328), 35. Retrieved from <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1121941/pdf/35.pdf>
- ⁴ Clinical_MRI_Chapter_14_8036XXP14Ap454-472.PDF. (n.d.). Retrieved September 29, 2014, from http://clinical-mri.com/wp-content/uploads/textbooks/clinical_mri/Clinical_MRI_Chapter_14_8036XXP14Ap454-472.PDF
- ⁵ Russell, E. J., Schaible, T. F., Dillon, W., Drayer, B., LiPuma, J., Mancuso, A., Maravilla, K., et al. (1989). Multicenter double-blind placebo-controlled study of gadopentetate dimeglumine as an MR contrast agent: evaluation in patients with cerebral lesions. *AJR. American journal of roentgenology*, 152(4), 813–23. Retrieved from <http://www.ajronline.org/doi/pdf/10.2214/ajr.152.4.813>
- ⁶ Brasch, R. C. (1985). Inherent contrast in magnetic resonance imaging and the potential for contrast enhancement. The 1984 L. Henry Garland lecture. *The Western Journal of Medicine*, 142(6), 847–53. Retrieved from <http://europemc.org/backend/ptpmcrender.fcgi?accid=PMC1306213&blobtype=pdf>
- ⁷ Runge, V. M., Clanton, J. A., Lukehart, C. M., Partain, C. L., & Jr., James, A. E. (1983). Paramagnetic agents for contrast-enhanced NMR imaging: a review. *AJR*, 141(6), 1209–1215. Retrieved from <http://www.ajronline.org/doi/pdf/10.2214/ajr.141.6.1209>
- ⁸ Brasch, R. C., Weinmann, H. J., & Wesbey, G. E. (1984). Contrast-enhanced NMR imaging: animal studies using gadolinium-DTPA complex. *American Journal of Roentgenology*, 142(3), 625–630. Retrieved from <http://www.ajronline.org/doi/pdf/10.2214/ajr.142.3.625>
- ⁹ Carr, D., & et al. (1984). Gadolinium-DTPA as a Contrast Agent in MRI: Initial Clinical Experience in 20 patients. *AJR*, August(143), 215–224. Retrieved from <http://www.ajronline.org/content/143/2/215.full.pdf>
- ¹⁰ Mann, J. S. (1993). Stability of gadolinium complexes in vitro and in vivo. *Journal of Computer Assisted Tomography*, 17 Suppl 1, S19–23. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/8486827>
- ¹¹ Cacheris, W. P., Quay, S. C., & Rocklage, S. M. (1990). The relationship between thermodynamics and the toxicity of gadolinium complexes. *Magnetic Resonance Imaging*, 8(4), 467–481. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/2118207>
- ¹² Ersoy, H., & Rybicki, F. J. (2007). Biochemical safety profiles of gadolinium-based extracellular contrast agents and nephrogenic systemic fibrosis. *Journal of Magnetic Resonance Imaging : JMRI*, 26(5), 1190–7. Retrieved from <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2709982/pdf/nihms109669.pdf>
- ¹³ Weinmann, H.-J., Brasch, R. C., Press, W.-R., & Wesbey, G. (1984). Characteristics of Gadolinium-DTPA Complex: A Potential NMR Contrast Agent. *AJR. American journal of roentgenology*, March(142), 619–624. Retrieved from <http://www.ajronline.org/content/142/3/619.full.pdf>
- ¹⁴ Magnevist FDA Approval History. (n.d.). Retrieved October 5, 2014, from http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory&#totable
- ¹⁵ Aime, S., & Caravan, P. (2009). Biodistribution of gadolinium-based contrast agents, including gadolinium deposition. *Journal of Magnetic Resonance Imaging*, 30(6), 1259–1267. Retrieved from

<http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2822463&tool=pmcentrez&rendertype=abstract>

- ¹⁶ Hao, D., Ai, T., Goerner, F., Hu, X., Runge, V. M., & Tweedle, M. (2012). MRI contrast agents: Basic chemistry and safety. *Journal of Magnetic Resonance Imaging*, 36(5), 1060–1071. Retrieved from <http://dx.doi.org/10.1002/jmri.23725>
- ¹⁷ Morcos, S. K. (2008). Extracellular gadolinium contrast agents: differences in stability. *European journal of radiology*, 66(2), 175–9. Retrieved from <http://www.sciencedirect.com/science/article/pii/S0720048X08000442>
- ¹⁸ Weinreb, J., & Amirbekian, S. (2013). Understanding Gadolinium-Based Contrast Agents: From the Molecule Up. Retrieved October 4, 2014, from http://www.medscape.org/viewarticle/780675_4
- ¹⁹ Tweedle, M. F., Kanal, E., & Muller, R. N. (2014). Considerations in the Selection of a New Gadolinium-Based Contrast Agent. *Applied Radiology, May Supple*, 1–11. Retrieved from <http://www.appliedradiology.com/articles/considerations-in-the-selection-of-a-new-gadolinium-based-contrast-agent>
- ²⁰ Runge, V. M. (2011). Conventional Contrast Agents (Gadolinium Chelates) v3 11-21-10 - ISMRM2011-8099.pdf. *Proc. Intl. Soc. Mag. Reson. Med.* Retrieved from <http://cds.ismrm.org/protected/11MProceedings/files/ISMRM2011-8099.pdf>
- ²¹ Idée, J.-M., Port, M., Robic, C., Medina, C., Sabatou, M., & Corot, C. (2009). Role of thermodynamic and kinetic parameters in gadolinium chelate stability. *Journal of magnetic resonance imaging : JMRI*, 30(6), 1249–58. Retrieved from <http://onlinelibrary.wiley.com/doi/10.1002/jmri.21967/abstract>
- ²² Laurent, S., Elst, L. Vander, & Muller, R. N. (2006). Comparative study of the physicochemical properties of six clinical low molecular weight gadolinium contrast agents. *Contrast Media & Molecular Imaging*, 1(3), 128–37. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/17193689>
- ²³ Frenzel, T., Lengsfeld, P., Schirmer, H., Hütter, J., & Weinmann, H.-J. (2008). Stability of gadolinium-based magnetic resonance imaging contrast agents in human serum at 37 degrees C. *Investigative Radiology*, 43(12), 817–28. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/19002053>
- ²⁴ Tweedle, M. F., Wedeking, P., & Kumar, K. (1995). Biodistribution of radiolabeled, formulated gadopentetate, gadoteridol, gadoterate, and gadodiamide in mice and rats. *Investigative Radiology*, 30(6), 372–80. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/7490190>
- ²⁵ Sieber, M. A., Pietsch, H., Walter, J., Haider, W., Frenzel, T., & Weinmann, H.-J. (2008). A Preclinical Study to Investigate the Development of Nephrogenic Systemic Fibrosis: A Possible Role for Gadolinium-Based Contrast Media. *Investigative Radiology*, 43(1). Retrieved from http://journals.lww.com/investigativeradiology/Fulltext/2008/01000/A_Preclinical_Study_to_Investigate_the_Development.9.aspx
- ²⁶ Pietsch, H., Pering, C., Lengsfeld, P., Walter, J., Steger-Hartmann, T., Golfier, S., Frenzel, T., et al. (2009). Evaluating the role of zinc in the occurrence of fibrosis of the skin: a preclinical study. *Journal of magnetic*

- resonance imaging : JMRI*, 30(2), 374–83. doi:10.1002/jmri.21845. Retrieved from <http://onlinelibrary.wiley.com/doi/10.1002/jmri.21845/abstract>
- ²⁷ Wollanka, H., Weidenmaier, W., & Giersig, C. (2009). NSF after Gadovist exposure: a case report and hypothesis of NSF development. *Nephrology Dialysis Transplantation*, 24 (12), 3882–3884. doi:10.1093/ndt/gfp494. Retrieved from <http://ndt.oxfordjournals.org/content/24/12/3882.full.pdf+html>
- ²⁸ Elmholdt, T. R., Jorgensen, B., Ramsing, M., Pedersen, M., & Olesen, A. B. (2010). Two cases of nephrogenic systemic fibrosis after exposure to the macrocyclic compound gadobutrol. *NDT Plus*, 3(3), 285–287. Retrieved from <http://ckj.oxfordjournals.org/content/3/3/285.full>
- ²⁹ Bayer HealthCare Pharmaceuticals. (n.d.). Magnevist Product Labeling (2014)-. Retrieved October 5, 2014, from http://labeling.bayerhealthcare.com/html/products/pi/Magnevist_PI.pdf
- ³⁰ Bracco Diagnostics Inc. (n.d.). ProHance Product Labeling (2013). Retrieved October 5, 2014, from http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020131s026,021489s003lbl.pdf
- ³¹ GE Healthcare. (n.d.). OMNISCAN (gadodiamide) Product Labeling (Aug. 2013) Retrieved October 5, 2014, from http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022066s00420123s039lbl.pdf
- ³² Mallinckrodt Inc. (n.d.). OptiMARK Product Labeling (2014). Retrieved October 5, 2014, from http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020937s023,020975s024,020976s025lbl.pdf
- ³³ Bracco Diagnostics Inc. (n.d.). MultiHance Product Labeling (2013)-. Retrieved October 5, 2014, from http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021357s013,021358s012lbl.pdf
- ³⁴ Bayer HealthCare Pharmaceuticals. (n.d.). Gadavist Product Labeling (2013). Retrieved September 25, 2014, from http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/201277s003lbl.pdf
- ³⁵ Guerbet. (n.d.). DOTAREM Product Labeling (2013). Retrieved September 25, 2014, from http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204781s000lbl.pdf
- ³⁶ Lantheus Medical Imaging. (n.d.). Ablavar Product Labeling (2013). Retrieved October 5, 2014, from http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021711s004lbl.pdf
- ³⁷ Bayer HealthCare Pharmaceuticals. (n.d.). Eovist Product Labeling (2013). Retrieved October 5, 2014, from http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022090s008lbl.pdf
- ³⁸ Grobner, T. (2006). Gadolinium--a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? *Nephrology, dialysis, transplantation : Official Publication of the European Dialysis and Transplant Association - European Renal Association*, 21(4), 1104–8. Retrieved from <http://ndt.oxfordjournals.org>
- ³⁹ Marckmann, P., Skov, L., Rossen, K., Dupont, A., Damholt, M. B., Heaf, J. G., & Thomsen, H. S. (2006). Nephrogenic Systemic Fibrosis: Suspected Causative Role of Gadodiamide Used for Contrast-Enhanced Magnetic Resonance Imaging. *J Am Soc Nephrol*, 17, 2359–2362. Retrieved from <http://jasn.asnjournals.org/content/17/9/2359.full.pdf>

- ⁴⁰ U.S. Food & Drug Administration. (2006). Postmarket Drug Safety Information for Patients and Providers - Public Health Advisory - Gadolinium-containing Contrast Agents for Magnetic Resonance Imaging (MRI). Center for Drug Evaluation and Research. Retrieved from <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm053112.htm>
- ⁴¹ U.S. Food & Drug Administration. (2007). Postmarket Drug Safety Information for Patients and Providers - Information for Healthcare Professionals: Gadolinium-Based Contrast Agents for Magnetic Resonance Imaging (marketed as Magnevist, MultiHance, Omniscan, Optimark, ProHance). UCM142884. Center for Drug Evaluation and Research. Retrieved from <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm142884.htm>
- ⁴² U. S. Food & Drug Administration. (2007) Postmarket Drug Safety Information for Patients and Providers - Public Health Advisory: Update on Magnetic Resonance Imaging (MRI) Contrast Agents Containing Gadolinium and Nephrogenic Fibrosing Dermopathy. Center for Drug Evaluation and Research. Retrieved from <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124344.htm>
- ⁴³ Office of the Commissioner. 2007 - FDA Requests Boxed Warning for Contrast Agents Used to Improve MRI Images. UCM108919. Retrieved from <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108919.htm>
- ⁴⁴ FDA Advisory Committees. (2009). Gadolinium-Based Contrast Agents & Nephrogenic Systemic Fibrosis - FDA Briefing Document - Advisory Committee December 8, 2009. (UCM190850.pdf). Retrieved August 2, 2012, from <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM190850.pdf>
- ⁴⁵ Center for Drug Evaluation and Research. Cardiovascular and Renal Drugs Advisory Committee - Slides for the December 8, 2009 Joint Meeting of the Cardiovascular and Renal Drugs and Drug Safety and Risk Management Advisory Committees. Retrieved from <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/ucm196216.htm>
- ⁴⁶ Cowper, S. E. (n.d.). Nephrogenic Systemic Fibrosis: History, Diagnosis and the Registry. UCM196233.pdf. Retrieved October 5, 2012, from <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM196233.pdf>
- ⁴⁷ Girardi, M., Kay, J., Elston, D. M., Leboit, P. E., Abu-Alfa, A., & Cowper, S. E. (2011). Nephrogenic systemic fibrosis: clinicopathological definition and workup recommendations. *Journal of the American Academy of Dermatology*, 65(6), 1095–1106.e7. doi:10.1016/j.jaad.2010.08.041 Retrieved from <http://www.sciencedirect.com/science/article/pii/S0190962210021468>
- ⁴⁸ Cowper SE. **Nephrogenic Systemic Fibrosis** [ICNSFR Website]. 2001-2013. Available at <http://www.icnsfr.org>. Accessed 10/05/2014.

⁴⁹ 2010 - FDA: New warnings required on use of gadolinium-based contrast agents. (n.d.). Retrieved from <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2010/ucm225286.htm>