Gadolinium based contrast agents (GBCA) used in MRI are extraordinarily safe, with less than 1 death per million administrations. That may be safer than driving to an MR imaging center which carries a 1 in a million risk of accidental death every 78 miles. However, a wealth of data on how to minimize these rare adverse events has emerged in the past few years and will be reviewed in this talk demonstrating GBCA to be among the safest contrast media.

**Dissociation/Transmetalation:** The chelate binding is strong for all GBCA, but stronger for macrocyclic compared to linear GBCA. Ionic linear chelates have stronger Gd binding compared to nonionic linear structures. This chelate-gadolinium binding can be characterized by kinetic stability and equilibrium thermodynamic stability. The nonionic linear agents especially when given in high doses to renal failure patients, have been associated with more interferences with serum laboratory testing, as well as with nephrogenic systemic fibrosis (NSF). Transmetalation is when another metallic ion such as zinc, iron, calcium or copper competes with gadolinium for the chelator binding site promoting gadolinium release into the serum and tissues.

**Biodistribution and Renal/biliary Excretion:** Although all GBCA are excreted renally, some linear ionic agents also have biliary excretion that allows for elimination even with renal failure. They also tend to have higher relaxivity so that they are administered at lower doses. These agents have no known unconfounded cases of NSF. Most GBCA redistribute into the extracellular compartment but one agent, gadofosveset, is retained in the blood pool by albumin binding, delaying renal/biliary excretion and allowing high SNR cardiovascular imaging. Although the longer elimination half-life of gadofosveset is worrisome, retention in the blood pool reduces tissue exposure; there are no known cases of NSF with gadofosveset.

**Toxicity:** Free Gd$^{3+}$ causes heavy metal poisoning but when administered with a chelator (as a GBCA) at routine clinical doses there is no toxicity.

**Adverse Event Reporting Incidences:** An accumulating body of literature is reporting a higher incidence of immediate allergic-type adverse events in females and patients with history of previous allergies especially to GBCA. Steroid prophylaxis may have a 30% breakthrough reaction rate suggesting this may not be an optimal preventive measure. Switching to another class of GBCA molecular structure and/or skin testing may be a useful preventive strategy in high risk patients with history of prior Gd reactions. Nonionic linear GBCA have the lowest immediate adverse event rate. Interestingly, pediatric and older patients have a lower incidence of both immediate allergic type reactions and NSF. In fact the youngest/oldest reported NSF patients are 6/87 year old suggesting that infant/toddlers and elderly are at low risk of NSF.

**Iron, Manganese, Barium….:** Other agents used in MRI have limited experience regarding safety.