Abstract: The bone cement and bone void filler market is crowded with new materials that broadly claim osteoconductive properties. However, the manner in which these materials balance structure, resorption, strength and biochemical factors is varied and all fall short of universal application. Evidence is provided demonstrating that the Kryptonite™ material provides a biochemical and structural environment suitable for osseous applications. A series of experiments are reviewed, including standardized biocompatibility tests defined by ISO 10993 and tests designed to assess the materials performance in clinically relevant models. Collectively these experiments demonstrate that the material is well tolerated by the body and presents no acute or long term risks to the recipient. Additionally, in some models the porous structure of the material lends itself to infiltration of new bone that persists through late time points and integrates with existing anatomy.

Motivated by the limitations of allografts, including finite supply, inadequate strength and concerns regarding disease transmission, numerous bone-graft substitutes that cure in situ have been developed in the lab and brought forward for clinical use. Although some success has been noted, no product has achieved universal acceptance as a substitute for allograft. Polymethyl-methacrylate materials have been used as bone replacement material because of their excellent mechanical strength. However, these materials are not conducive to regeneration of bone, are not resorbable, and impose chemical and thermal challenges to local tissue at the time of implantation. Tri-calcium phosphates and similar cements have received attention due to their bioabsorption, biocompatibility, and isothermic properties. These materials; however, do not perform as well as native bone in many loading configurations and cannot be used as a standalone remedy in load bearing applications. Rapid rates of resorption may in some instances exceed the rate of proper bone ingrowth that results in an overall weakened construct. Product failures, generally associated with tensile loads or material fatigue, have limited widespread acceptance and prevented these materials from supplanting autograft as the standard of care for procedures requiring bone regeneration.

The Kryptonite™ material is a polymer comprised of castor oil based polyols, a reactive isocyanate and calcium carbonate powder that cures in situ. Three component parts are mixed intraoperatively to form a viscous liquid, which polymerizes over approximately 20 minutes, transforming from an injectable state, through an adhesive taffy-like paste, to a moldable putty (Figure 1). Over the next 24 hours polymerization continues, ultimately forming a rigid polymer. One of the chemical reactions generates carbon dioxide gas, which remains entrapped within the viscous material and forms a porous network resembling human cancellous bone.

Figure 1: As it polymerizes the Kryptonite material transitions from an injectable viscous liquid to a sticky taffy-like consistency, to a moldable putty and ultimately to a rigid solid.

The Kryptonite™ material is manufactured by Doctors Research Group, Inc. (Southbury, CT) and was first used in Europe in 2006. Through 2009, the material has been used in more than 3000 clinical cases and no adverse events related to biocompatibility have been reported. The material has received FDA marketing authorization for cranial applications and is CE marked (see the package insert for market specific Indications for Use). Figure 2 depicts use of the material for filling a cranial defect that resulted from a motor vehicle accident. In this case the material was applied in the sticky, taffy-like state and contoured to fit the surrounding bone. A description of the surgical technique and reports on early clinical experience in cranioplasty applications are available from Doctors Research Group.³²

Figure 2: The Kryptonite material can be applied to defects of the skull.

To be effective, a bone void filling device must exhibit two key features; a favorable chemical environment and an appropriate structure. This article presents evidence that the Kryptonite material meets both criteria from several sources of scrutiny. First, a review of published literature pertaining to implantable castor oil polymers reveals the high potential for this class of material to serve as a biocompatible bone filler.
Second, the chemical analysis of the Kryptonite material demonstrates that no unexpected, potentially harmful chemical residuals are present in the material. Third, a review of the in vitro and in vivo biocompatibility testing further supports the safety of this novel material. Next, analysis of the material’s geometry addresses how its porosity relates to inherent potential for osseointegration. Finally, several animal studies demonstrate the interplay between the Kryptonite material and the adjacent bony environment. With the positive experiences from thousands of human clinical case applications it is easy to forget the extensive bench top and animal testing conducted to demonstrate the safety and efficacy of this material. These summaries have been collected to provide sufficient information for the clinician to have confidence in the safety of this material as well as understand clear advantages that the Kryptonite material offers over other bone cement / void filler products.

**Literature Review**

Studies defining the biocompatibility of implantable polymers derived from castor oil have been published as early as 1995. These studies evaluated this class of material in various forms and formulations in a variety of animal models. Several of these studies are summarized below. In each, the authors conclude that the subject materials are biocompatible, non-toxic and suitable for filling bone voids.

**Segmental Radial Defect (Rabbit)** – Granules formed from castor oil based polymer were mixed with blood and applied to segmental defects in adult rabbits. The defects were radiographically assessed at time points through 120 days. Although not as effective as autograft, the castor oil based polymer did show 79% new bone formation. Histological examination showed that the material minimized local production of fibrous tissue, maintained its structure (i.e. did not resorb) and did not initiate an inflammatory reaction.

**Zygomatic Defect (Rabbit)** - 5mm zygomatic bone defects in adult rabbits were filled with castor oil based polymer discs. The animals were evaluated along a series of time points through 90 days and the pathology was analyzed. Although fibrous tissue encapsulated the material, no inflammation was observed. The authors also reported acidophilic and basophilic areas inside the micropores of the material that suggested cellular infiltration.

**Alveolar Bone Defect (Canine)** – A castor oil based polymer resin was delivered to bony defects following tooth extraction in a canine model. The authors reported that the material was replaced by different maturities of bone tissue and that no immune or inflammatory reactions were detected.

This historical experience demonstrates the biocompatibility of this general class of material, and also suggests that new castor oil-based polymers sharing the basic chemistry of these predicates have a high probability of exhibiting similar biocompatibility. That said, it is paramount to validate this assumption through comprehensive in vitro and in vivo testing. Additionally, testing of a new material will fully characterize structural properties including porosity and resorption profile. These and other critical properties may be manipulated through subtle formulation and processing changes to accentuate the desired clinical product.

**Chemical Analysis**

The chemistry used to create the Kryptonite material is very different from traditional bone cements (e.g. PMMA, TCP, HA). A condensation reaction is used to form polymer chains, carbon dioxide gas is generated and used to form the materials ‘bone-like’ structure, and intermediate reactions balance the target working time and final mechanical properties. In systems where multiple simultaneous reactions are occurring, it is critical to verify that the product does not contain contaminants or yield potentially toxic or biologically incompatible residuals following the final polymerization. This validation process is no different from the analyses that traditional bone cements must undergo, and in fact direct comparisons with such products were required to support the regulatory approval of the Kryptonite material. Several of the most critical tests have been summarized below. These studies were conducted by independent laboratories according to well-defined protocols. Many of these studies utilized a chemical extract from the Kryptonite product, in which the material is mixed, allowed to partially polymerize and then submerged in a solvent for a period of time. Chemical components not fully incorporated into the bulk material diffuse into the solvent and the solution is analyzed using a variety of techniques.

**Extractable MDA** – The reactive chemical in the Kryptonite prepolymer component is methylene diphenyl diisocyanate (MDI). During an intermediate step in the polymerization process some MDI reacts with water to form methylene dianiline (MDA). In certain doses MDA can have harmful effects, so the chemical formulation of the Kryptonite product was beentoachimetrically balanced to minimize the presence of residual MDA monomer in the final product. High

![](image)

*Figure 3: Radiographs from radial defect in rabbit treated with granular castor oil based polymer. Images taken at 0, 15, 30, 60 and 120 days.*

Mandibular Defect (Rat) - Granular castor oil based polymer was applied to cylindrical mandibular defects in a rat model. By 45 days there was evidence of maturation of collagen fibers and early lamellar bone formation. Both the polymer and the demineralized bone graft control demonstrated adequate stability, sufficient stimulation of osteogenic connective tissue, and infiltration of vasculature support.
performance liquid chromatography was used to analyze Kryptonite extract following a 24-hour soak in both saline and toluene. Measured levels were below 0.5 ppm, which represents an equivalent exposure level to five liters of drinking water. ³

Trace Metals / Elements – Aqueous extracts were collected from the Kryptonite material during the polymerization process and after final cure. Inductively coupled plasma spectroscopy showed that, with the exception of calcium and potassium, all elements analyzed were present in concentrations below 0.5 ppm.

Physicochemical Study – Non-volatile residue, residue on ignition, heavy metals as lead and buffering capacity studies were conducted according to USP protocols. All results met the USP limits, indicating that no significant extractable elements were present in the Kryptonite material.

Degradation – Specimens of the Kryptonite material and a PMMA cement were soaked in water at elevated temperature for 2 and 60 days to assess the material degradation. No significant mass loss or swelling was measured for either material, nor was any visual wear debris noted.

Biocompatibility Testing

The International Standards Organization (ISO) has published guideline ISO-10993 which defines a series of tests used to evaluate the biocompatibility of new materials prior to human clinical use. These tests are conducted according to strict protocols, and, in the case of the Kryptonite material, were conducted by independent laboratories specializing in medical device studies. In addition to these standard tests, non-standard tests were also conducted to directly address specific biocompatibility aspects of the material. In some cases these tests differed from the ISO-10993 standard with respect to a larger sample population or in selecting an alternate control material. Although not explicitly stated in each of the following summaries, all tests were conducted with one or more controls.

Maximization Sensitization Study (Part 10) – This study evaluated the potential for delayed dermal contact sensitization using a guinea pig model. Chemical extract from the Kryptonite material was injected intradermally and then occlusively patched in an attempt to induce sensitization. Challenge patches were applied a second time after an initial recovery period. The Kryptonite material showed no evidence of contact sensitization either acutely or delayed.

Intracutaneous Study (Part 10) – Intracutaneous injections of chemical extracts were made in the backs of adult rabbits. The injection sites were observed immediately after injection and evaluated for erythema and edema at time points through 72 hours. All the injection sites appeared normal immediately following injection and the Primary Irritation Index characterization was negligible.

Systemic Toxicity Study (Part 11) – A chemical extract from Kryptonite material was injected into mice by either intravenous or intraperitoneal route and the animals were observed through 72 hours for systemic effects. There was no evidence of significant systemic toxicity from the extracts.

Pyrogen Study (Part 11) – Chemical extract from Kryptonite material was intravenously injected via the marginal ear vein in a rabbit model. Rectal temperatures were measured through three hours after injection and judged to be nonpyrogenic.

Muscle Implantation Study (Part 6) – Kryptonite material was implanted into paravertebral muscles of adult rabbits. At two weeks the animals were sacrificed and the paravertebral muscles were dissected and processed for microscopic evaluation. The macroscopic reaction was not significant and microscopically the Kryptonite material was classified as only a slight irritant compared to a polyethylene control.

In Situ Curing Measurements – Kryptonite material in the liquid state was injected into the paravertebral muscle of rabbits to assess the setting time, curing reaction and temperature rise during the polymerization process. One hour after implantation the animals were euthanized and local tissue was harvested for macroscopic and microscopic evaluation. A peak temperature of 37.7°C was measured 19 minutes after delivery with no evidence of thermal damage. No disintegration or particle separation was noted.

Genotoxicity: In Vitro Chromosomal Aberration Study – Extract of the Kryptonite material was introduced to a monolayer of Chinese Hamster Ovary (CHO) cells in either the presence or absence of S9 metabolic activation to assess genotoxicity. Following culture, a microscopic examination was conducted for chromosomal aberration. The Kryptonite extract was not considered genotoxic.

Genotoxicity: Bacterial Reverse Mutation Studies (Part 3) – A salmonella typhimurium and Escherichia coli reverse mutation standard plate incorporation study was conducted on several Kryptonite extracts to evaluate whether mutagenic changes in the average number of revertants would occur. The extract did not inhibit growth of the test strains and was considered nonmutagenic.

Bone Marrow Micronucleus Study (Part 3) – Mice were injected intraperitoneally with Kryptonite extract and observed immediately following injection and for three subsequent days. The mice were euthanized, femoral bone marrow was collected, and smears were prepared and analyzed. There was no increase in micronucleated polychromatic erythrocytes, and as a result the material was not considered genotoxic.

In Vitro Hemolysis Study – Rabbit blood was pooled, diluted and added to Kryptonite extract. After mixing, the suspension was allowed to stand for 4 hours and then centrifuged. A reagent was added to the resulting supernatant and the percent transmission was spectrophotometrically quantified as having a hemolytic index of 0%, meaning the extract was nonhemolytic.
26 Week Carcinogenicity Study in Transgenic ras H2 Mouse Model – Kryptonite material was evaluated for the potential to induce tumor formation (cancer) following subcutaneous implantation in a transgenic mouse model. Material was implanted over the skull and parallel to the lumbar and thoracic vertebral column. Animals were routinely examined through 26 weeks. Upon sacrifice, a detailed necropsy was conducted and selected tissues were histologically evaluated. The results showed no evidence of increased tumorigenicity.

Mouse Lymphoma Mutagenesis Assay – Kryptonite extract was tested for its potential to induce an increase in the number of homozygous thymidine kinase (TK-/-) mutants in the presence and absence of a metabolic activation system. The results showed no significant increase in the frequency of homozygous mutants in cells exposed to the Kryptonite extract. The material was considered non-mutagenic under the experimental conditions.

Neurotoxicity in Rabbit Model – 8-mm diameter cranial defects were created in adult rabbits and filled with Kryptonite material in the malleable putty state. The animals were sacrificed at 12 weeks and skull bone and underlying brain tissue were macroscopically and microscopically evaluated for inflammation, encapsulation, hemorrhaging, necrosis and discoloration. No pathology was observed. Bone resorption and remodeling was similar for the Kryptonite material and PMMA control sites. The study concluded that the material was well-tolerated and resulted in no significant findings in the underlying brain tissue.

26 Week Subchronic and Acute Toxicity Study – Kryptonite material was implanted within two subcutaneous pockets created in male rats. The rats were observed and weighed on a daily basis for 26 weeks. At sacrifice a battery of hematology parameters were analyzed, including 18 clinical chemistry parameters on the serum fraction. The organs were harvested and processed for histopathology where inflammation and healing responses were assessed microscopically. No biologically meaningful differences were noted for any of the hematomatologic or clinical chemistry parameters in a comparison of the Kryptonite material and PMMA control arms. No significant signs of inflammation, encapsulation, hemorrhage, necrosis, or discoloration were noted, resulting in a bioactivity rating of ‘No Reaction’. The study concluded that the Kryptonite material did not demonstrate any local or systemic signs of toxicity after long-term implantation.

Collectively these in vitro and in vivo tests demonstrate the biocompatibility of the Kryptonite material, meaning that the material itself does not provide a short term or long term risk to the patient. With the establishment of safety, the next series of studies are aimed at demonstrating the efficacy of the Kryptonite ‘device’ in meeting its intended clinical use.

Structure and Porosity

The formation of pores through the generation of carbon dioxide results in a structure unique to the bone cement / void filler market. In an effort to better understand the potential clinical impact of this structure on osseointegration, a series of experiments were conducted. The Kryptonite material was imaged using microCT at an 8μm pixel resolution. The planar data was compiled to form 3D representations and analyzed using validated software to provide quantitative morphological information. This technique is recognized in the literature as an effective means of analyzing porous scaffolds. Figure 4 shows the predominantly closed pore structure of the Kryptonite material, with a thin film of polymer separating one pore from the next; often less than 10-μm thick. The majority of pores range from 50 to 300 μm in diameter, with a mean diameter of approximately 150 μm. Numerous studies have investigated the structural requirements that are necessary to allow cell migration and new bone growth. Although these studies focus on a variety of different materials, geometric structures and applications, they generally agree on a minimum pore size of approximately 100 μm. With the majority of the Kryptonite material’s pores exceeding this minimum, this analysis suggests that the structure is favorable for osseointegration.

![Figure 4: MicroCT image showing carbon dioxide filled pores (black) within Kryptonite material (gray). Clumps of calcium carbonate filler are also visible (white).](image)

![Figure 5: Histogram depicting distribution of pore sizes, with mean centered at 150 microns.](image)

Through microCT analysis and direct measurement of volumetric expansion it is understood that the bulk Kryptonite material is composed of approximately 50% carbon dioxide gas. However, further evaluation of the Kryptonite material’s porosity using pycnometer revealed an interconnected porosity of less than 5%. This difference between the measured interconnected porosity and the total carbon dioxide content demonstrates that a significant percentage of the pores are not
interconnected and thus not available for immediate infiltration by host cells. Thus, in order to allow unobstructed bone ingrowth it is critical that the initially closed pore structure be converted to a predominantly open structure. Earlier degradation studies showed that the Kryptonite material is stable in an acellular environment. More specifically, no significant hydrolytic degradation was measured during the studies, eliminating this simple mechanism as a means for structural conversion. To determine whether a more complex, biologic process could affect the interconnectivity, Kryptonite material was exposed to cell culture and the interaction was observed. Osteoclasts were obtained from the long bones of mice, concentrated in solution, delivered over a Kryptonite wafer (15-mm x 2mm thick) and cultured in an incubator at 37°C and 5% CO₂. Osteoclast viability was monitored daily and the media was replenished as necessary. After two weeks the Kryptonite wafers were removed from culture and analyzed with a digital microscope.

Visual inspection of the wafers revealed that the ‘skin coat’, the thin, non-porous layer of material that forms on the exposed surfaces due to surface tension effects, had been removed under osteoclast culture and exposed the underlying pores (Figure 6). Backlit images allowed irregular edge geometry in the newly formed openings to be appreciated as different from the typically smooth circular edges forming CO₂ pores. This suggested that the surfaces were substantially altered by the osteoclasts (Figure 7). This observation supports a hypothesis that the in vivo environment provides a mechanism for the elimination of the thin film between pores, locally converting the initially closed pore structure to an open pore structure. With successful demonstration in a bench top model, the next step in validation will be to evaluate a more clinically relevant animal model.

The biocompatibility studies presented earlier in this report demonstrated that the Kryptonite material poses no potential health risk to the patient. However, they do not specifically assess the degree to which host bone integrates with the Kryptonite material. As suggested in the previously described imaging and cell culture studies, the Kryptonite material possesses a unique, potentially advantageous, structure for providing long term biological and mechanical stability. The following studies investigate the osseointegration and stability in a variety of animal models.

**Mouse Femoral Defect** – Adams *et al* used microCT and dual promoter-GFP reporter transgenic mice to allow visual detection of osteoblasts infiltrating Kryptonite material that has been implanted within the distal metaphysis of the femur, a site of progressive age-related bone loss. The mice carried both a rat 3.6 kb type I collagen promoter driving a cyan fluorescent protein and a human 3.9 kb osteocalcin promoter driving a toapz fluorescent protein. Mice were aged to 6-8 weeks prior to implantation. Lateral 1mm diameter holes were drilled bilaterally in the distal femoral metaphyses and either left unfilled to serve as a repair control, filled with the Kryptonite material, or filled with PMMA. Mice were sacrificed at early time points (2 weeks, 1 month, 2 months and 3 months) and late time points (12 and 15 months). 24 hours prior to sacrifice each animal was injected with xylene orange to label bone formation. Femurs were harvested and fixed in 10% buffered formalin. The test region was imaged using microCT (Scanco μCT40) at a resolution of 12 microns. Specimens were placed in 30% sucrose for 24 hours, embedded in OCT, and stored at 20°C. Longitudinal sections were obtained at 5 μm thickness using a cryotome and tape-transfer system (cryoJane). Arrays of high resolution digital images were captured and superimposed for each fluorescent filter and stitched into mosaics using a Zeiss fluorescent microscope workstation. The sections were re-imaged after staining with von Kossa silver nitrate to label bone mineral and a fluorescent tartrate resistant acid phosphatase (TRAP) stain was employed to label osteoclasts.

Unfilled holes demonstrated reconstitution of cortex and trabeculae by 1-2 months (male mice). Trabecular structure at the repair site was diminished but present in male mice through 12 months, whereas in females the loss of trabeculae outpaced healing such that the trabecular structure vanished by 3 months. Appositional bone formation was present within the Kryptonite material at 1 month in both male and female mice and persisted beyond 12 months. Active formation within the porosity, as indicated by the xylene orange label was coincident with immature osteoblasts marked by the type I collagen reporter and at late time points with mature osteoblasts marked by the osteocalcin reporter. Osteoclasts were present within the scaffold by 3 months, but the Kryptonite material showed no evidence of scaffold degradation.

**Osseointegration**

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Figure 8: Micro CT section showing persistent bone growth throughout Kryptonite at 18 months post-op (left) and no bone ingrowth in a PMMA filled void (right).

Figure 9: Ingrowth of cortical like bone inside pores within the Kryptonite material implanted in a mouse femur.

The results of this study support the theory that the Kryptonite material provides both a favorable biochemical environment for osseointegration and a favorable structure. Further evaluation in a larger animal model will additionally address questions regarding how scale, application site and loading affect the rate at which this osseointegration occurs and the relevance to human clinical applications.

Posterolateral Fusion in Rat – The efficacy of the Kryptonite material for inducing posterolateral spinal fusion was assessed in a Lewis rat model by Lee et al.\textsuperscript{,12} Eight rats were included in each of three groups: Kryptonite material, autograft and a sham surgery. The transverse processes of L4 and L5 were decorticated and 0.3 cc of graft or test material were placed bilaterally. Radiographs taken at 3 days, 2 weeks, 4 weeks, 6 weeks and 8 weeks were blinded to the evaluator. Each x-ray was graded on the degree of fusion using a 0-4 scoring system (Figure 10). After 8 weeks the rats were sacrificed and the spines were harvested.Manual palpation was performed to characterize the spines as either fused or not fused. By eight weeks all of the rats treated with Kryptonite product were fused based on both the radiographic and palpation assessments. Only minimal radiographic evidence existed for bone formation in the autograft or sham surgery controls, and none of these were judged to be fused.

36-Week Rabbit Calvarial Defect – Two bilateral defects (15mm x 8mm) were created in the calvarium of twenty-four adult New Zealand white rabbits. The defect was positioned 2-mm posterior to the transverse bone sutures between the frontal and parietal bone and 3mm lateral to the midline. Care was taken to avoid perforating the dura, but small dural tears did occur. The defects were filled with either the Kryptonite material or hydroxyapatite cement (BoneSource, Stryker Corp). Rabbits were sacrificed at four time points (12, 18, 24, 36 weeks).

Macroscopic evaluation revealed that the expected expansion of the Kryptonite material had occurred. Only minimal invagination of the cranial vault was noted with no apparent injury to the underlying tissue. At the 12-week time point the hydroxyapatite control specimens showed infiltration of new bone. Although new bone was not present in all Kryptonite specimens, where new bone was observed, it presented in the absence of extensive autolysis or inflammatory response. At both the 18 and 24-week time points bone formation was evident and progressively expanding within the margins of the Kryptonite material. Evidence of implant resorption within its

Figure 10: Representative radiographs for control (left) and Kryptonite material (right) at 8 weeks after posterolateral fusion procedure.

Figure 11: Bone growth evident several millimeters within Kryptonite material in rabbit calvarial model at 36 weeks.
internal structure was common. The implant margins maintained contact with the surrounding host bone and appeared structurally stable. By 36 weeks the control hydroxyapatite material had been nearly completely resorbed. The Kryptonite material was still present and remained fully integrated with bone. Both materials formed similar lamellar bone architecture with clear trabecular morphology and adequate vascular support.

**Discussion/Conclusion**

The Kryptonite material has been qualified through extensive investment in careful research and development. That focus has demonstrated the safety and efficacy of this novel biomaterial. Its unique properties include adhesiveness, porous structure and cancellous bone-like stiffness and low exothermic curing. These important properties clearly differentiate it from other products in the bone cement / void filler market and provide compelling reasons for its clinical use.

**References**

Unless otherwise noted all data is on file at Doctors Research Group.

9. Lins, AS; Barrows, TH; Carmell, SH; Guldberg, RE, “Microarchitectural and mechanical characterization of
Kryptonite™ material has received a CE mark for use in Europe as a self-setting bone filler for long voids or gaps that are not open to the stability of the bone structure. Kryptonite™ material is a resorbable material for the repair of bone defects that may be shaped and gently applied to cranial defects. Kryptonite™ material has received clearance in Australia (TGA) and in Canada (Health Canada Approved).

Kryptonite™ material has also received marketing authorization from the United States Food and Drug Administration as a bone cement with indications for use as a resorbable material for filling cranial defects.

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