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PEEK Biomaterials in Trauma, Orthopedic, and Spinal Implants

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Abstract

Since the 1980s, polyaryletherketones (PAEKs) have been increasingly employed as biomaterials for trauma, orthopedic, and spinal implants. We have synthesized the extensive polymer science literature as it relates to structure, mechanical properties, and chemical resistance of PAEK biomaterials. With this foundation, one can more readily appreciate why this family of polymers will be inherently strong, inert, and biocompatible. Due to its relative inertness, PEEK biomaterials are an attractive platform upon which to develop novel bioactive materials, and some steps have already been taken in that direction, with the blending of HA and TCP into sintered PEEK. However, to date, blended HA-PEEK composites have involved a trade-off in mechanical properties in exchange for their increased bioactivity. PEEK has had the greatest clinical impact in the field of spine implant design, and PEEK is now broadly accepted as a radiolucent alternative to metallic biomaterials in the spine community. For mature fields, such as total joint replacements and fracture fixation implants, radiolucency is an attractive but not necessarily critical material feature.

Keywords

PEEK; PAEK; Ultrapek; polyaryletherketone; polyetherketone; polyetheretherketone; composites; carbon fiber; wear; hip resurfacing; spine; fracture fixation; mechanical behavior; physical properties; tribology; biocompatibility; review

Introduction

Following confirmation of its biocompatibility two decades ago [1], polyaryletherketones (PAEKs) have been increasingly employed as biomaterials for orthopedic, trauma, and spinal implants. Commercialized for industry in the 1980s, PAEK is a relatively new family of high temperature thermoplastic polymers, consisting of an aromatic backbone molecular chain, interconnected by ketone and ether functional groups [2]. Two PAEK polymers, used previously for orthopedic and spinal implants, include poly(aryl-ether-ether-ketone) (PEEK) and poly(aryl-ether-ketone-ether-ketoneketone) (PEKEKK) (Fig. 1). The chemical structure of polyaromatic ketones confers stability at high temperatures (exceeding 300°C), resistance to chemical and radiation damage, compatibility with many reinforcing agents (such as glass and

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carbon fibers), and greater strength (on a per mass basis) than many metals, making it highly attractive in industrial applications, such as aircraft and turbine blades, for example [2,3].

Historically, the availability of polyaromatic polymers arrived at a time when there was growing interest in the development of “isoelastic” hip stems and fracture fixation plates, with stiffnesses comparable to bone [4]. Although neat (unfilled) polyaromatic polymers can exhibit an elastic modulus ranging between 3-4 GPa, the modulus can be tailored to closely match cortical bone (18 GPa) or titanium alloy (110 GPa) by preparing carbon fiber reinforced (CFR) composites with varying fiber length and orientation [4]. In the 1990s, researchers characterized the biocompatibility and in vivo stability of various PAEK materials, along with other “high performance” engineering polymers, such as polysulphones and polybutylene terephthalate [5]. However, use of these polymers in implants was abandoned for reasons that are not well documented in the literature. Other polyaromatic ketone polymers, such as PEKEKK, were discontinued by their industrial supplier and thus ceased to be available for biomaterial applications.

By the late 1990s, PEEK had emerged as the leading high performance thermoplastic candidate for replacing metal implant components, especially in orthopedics [6,7] and trauma [8,9]. Not only was the material resistant to simulated *in vivo* degradation, including damage caused by lipid exposure, but starting in April 1998 PEEK was offered commercially as a biomaterial for implants (Invibio, Ltd.: Thornton Cleveleys, United Kingdom). Facilitated by a stable supply, research on PEEK biomaterials flourished and is expected to continue to advance in the future [10].

Numerous studies documenting the successful clinical performance of polyaryletherketone polymers in orthopedic and spine patients continue to emerge in the literature [11-16]. Recent research has also investigated the biotribology of PEEK composites as bearing materials and flexible implants used for joint arthroplasty [17-20]. Due to interest in further improving implant fixation, PEEK biomaterials research has also focused on compatibility of the polymer with bioactive materials, including hydroxyapatite, either as a composite filler, or as a surface coating [21-26]. As a result of ongoing biomaterials research, PEEK and related composites can be engineered today with a wide range of physical, mechanical, and surface properties, depending upon their implant application.

The versatility of PEEK biomaterials necessarily translates into increased complexity, both for implant designers, as well as for researchers seeking to explore new modifications of PEEK for novel implant applications. In recent years, advances in the processing and biomaterials applications of PEEK have been progressing steadily. However, much of the previous research on PEEK implants has been fragmented in the materials science, composites, biomaterials, and application-specific literature. Consequently, the primary goal of this review is to synthesize the disparate repositories of data to provide a comprehensive, state-of-the-art assessment of PEEK and PEEK composites as a family of biomaterials. As background for this review, we first provide a summary of polyaromatic ketones as the basis for understanding the chemical, physical, and mechanical properties for this family of polymeric biomaterials. The second part of this paper summarizes the biocompatibility and in vivo stability of PEEK. Although a thorough treatment of all types of PEEK implants is beyond the scope of this paper, we conclude with an overview of the clinical applications of PEEK and related polyaromatic ketones in the orthopedics, trauma, and spinal literature.

Structure and Properties of Polyaryletherketone Polymers

Developing an understanding of structure and properties of PAEKs necessarily must be accompanied by some consideration of the polymerization process, the amorphous and crystalline phases in the material, as well as processing effects and the effects of fillers, such

as carbon fiber. In the following sections, we have reviewed the polymer chemistry, industrial nomenclature, and polymer structure. We also summarize the chemical and mechanical properties of PAEK materials and their industrial composites, with an emphasis on PEEK and industrial resins that have been adopted for use in implants. Readers already familiar with the basic science of PAEK polymers may wish to skip ahead to sections devoted to biocompatibility, bioactive composites, and implant applications.

Polymerization of Polyaryletherketones

Historically there have been two main routes involved in the production of PAEKs. The first method involved linking aromatic ether species through ketone groups, whereas a second method involves linking aromatic ketones by an ether bond. The first method involves an reaction and Friedel Crafts acylation chemistry whereas the second route involves a nucleophilic displacement reaction.

The electrophilic synthesis of PAEK polymers produces materials with reactive end groups such as benzoic acids. Such polymers cannot be processed, without end-capping, due to their high thermal instability. More recently a modification to the electrophilic process for manufacturing PAEK polymers has been described [27]. This electrophilic route permits the manufacture of thermally stable PAEK polymers and has been utilized in industrial processes.

The nucleophilic route to PAEK polymers, patented by ICI in 1977, provides another pathway to polymers such as PEEK. The establishment of the nucleophilic route to PAEK polymers permitted the investigation of polymer variants by the use of different bisphenols to produce PAEK polymers with various properties as reported by Attwood et al. [28]. The family of PAEK polymers grew to contain variants such as PEK, PEEK, PEKK, PEKEKK, etc., with a range of glass transition temperatures (143-160°C) and high crystalline melt temperatures (335-441°C).

PEEK represents the dominant member of the PAEK polymer, and can be processed using a variety of commercial techniques, including injection molding, extrusion and compression molding, at temperatures between 390°C and 420°C. At room and body temperature, PEEK is in its “glassy” state, as its glass transition temperature occurs about 143°C, whereas the crystalline melt transition temperature (T_m) occurs around 343°C. After polymerization, PEEK is chemically inert and insoluble in all conventional solvents at room temperature, with the exception of 98% sulphuric acid [26].

Nomenclature

The literature on PAEK resin is a maze of trade names and producers, which have changed over the years, complicating interpretation of published data for today's materials. For researchers interested in deciphering the historical polymer science literature, we provide here a brief primer on the nomenclature of PAEK resins used for industrial purposes as well as for biomaterials (Table 1). Sustainability of biomaterial supply and consistency in nomenclature has been a concern with PAEK resins in the 1980s and 1990s. To the extent that biomaterials history is not fully reflected in the literature, Table 1 provides some guidance as to the current availability (or lack thereof) of PAEK materials for industrial and implant use.

Resin, when used in the context of this review, refers to the neat, unfilled powder that is created by polymerization, whereas grades are typically characterized by flow characteristics (e.g., for injection molding or compression molding) or based on their filler content (e.g., glass fiber or carbon fiber). Because PAEK polymers are converted using standard thermoplastic processing techniques, such as injection molding, extrusion, and compression molding. The polymer is

also available in pellet and powder form. Powder grades are recommended for compounding, whereas granulated resin is preferred for injection molding.

Historically, PAEK materials, including PEEK, have been produced primarily as niche polymers for industrial use, because their cost even today is at least two orders of magnitude more expensive than low-temperature thermoplastics such as polyethylene. When ICI launched Victrex PEEK in 1987, the primary application targets were not medical. However, Victrex PEEK was used, if not yet supported, for implant applications. The Victrex PEEK business was sold by ICI in 1993, and in 1998 Victrex launched PEEK-OPTIMA for long-term implantable applications. In 2001 Victrex established Invibio Biomaterial Solutions to specifically provide grades of PEEK suitable for long-term implantation. The nomenclature for the Victrex/Invibio resin grades has changed over time, but the polymerization technology and molecular weight range used for the various grades has remained fundamentally similar (Table 2).

Crystalline Structure, Morphology, and Thermal Transitions

PEEK conforms well to the conceptual model of a two-phase semi-crystalline polymer, consisting of an amorphous phase and a crystalline phase. Like many semi-crystalline polymers, including ultra-high molecular weight polyethylene (UHMWPE), the crystalline content of PEEK varies depending upon its thermal processing history. However, in many ways, the crystallization behavior of PEEK is more complex than UHMWPE, which is far above its glass transition temperature ($T_g = -80$ to -120°C) when the polymer is used at room and body temperature. The crystallization of PEEK has been shown to be very similar to polyethylene terephthalate (PET) [29].

The crystalline content of injection-molded PEEK in implants typically ranges from 30 to 35%, however a broader range (0-40%) can be encountered with this material, depending upon how it has been processed. For example, purely amorphous PEEK films can be routinely produced by supercooling thin samples (<1 mm sections) from the melt by immersion in cold water [29]. On the other hand, partially amorphous PEEK can also form locally near the surface of larger, injection-molded components, forming a thin amorphous “skin,” if the surface material is cooled too quickly from the melt [30].

With a bond angle of 125° , the PEEK molecular chain favors a zig-zag conformation (Fig. 2A) that can form crystallites [31]. Based on x-ray diffraction studies, “c” long-axis of the orthorhombic unit cell of PEEK spans three aryl groups, with a center-to-center distance between aryl groups of 5 Å, corresponding to a long-axis length of 15 Å (Fig. 2B) [31]. The size of the ketone and ether groups in the molecular chain are comparable, so that the tendency of polyaryletherketones to crystallize is only subtly influenced by chemical structure. For example, the crystalline density of PEEK and PEK differ by only 0.03 g/cc [31].

PEEK crystals consist of very fine *lamellae* that under certain conditions can organize into larger *spherulites* [32]. The thickness of lamellae, as well as the size and density of spherulites, depends on the processing conditions from the melt [29]. The lamellar thickness of melt-crystallized PEEK is extremely small, only 50 and 60 Å [29], corresponding to 10-12 aryl groups. Spherulites are orders of magnitude larger, about 25 to 40 μm in diameter [29]. The spherulitic microstructure of PEEK can be visualized using scanning electron microscopy with suitable etching [33], or by polarized light microscopy [29,32]. Depending upon the nucleation density and processing conditions, it may not be possible to identify individual spherulites using polarized light microscopy. Instead, the morphology under polarized light may have the appearance of a “fine grained mosaic structure” of crystalline domains with varying birefringence [34].

Because of the relationship between mechanical properties and crystallinity, it is useful to characterize the crystalline content of implant components fabricated from PEEK [35]. However, the actual size and extent of crystals in PEEK is a function of a number of variables, including processing temperature, time, the localized cooling rate (which depends upon the thickness of the processed part), and any post-production annealing [30]. Furthermore, if the temperature varies substantially as a function of location in an implant component as it is cooled from the melt, the crystallinity may be spatially heterogeneous, with the surface “skin” exhibiting potentially lower crystallinity than the bulk core [30]. The introduction of composite fillers, such as carbon fiber, to PEEK can provide additional nucleation sites within the polymer, further complicating analysis of its crystallinity [35].

Crystallization occurs in amorphous PEEK at temperatures approaching T_g ($\sim 143^\circ\text{C}$) but still far below the principal crystalline melt transition at 335°C . For industrial applications, which can expose PEEK to continuous temperatures of up to 250°C , operating near or above T_g can induce in-service crystallization (also referred to as “physical aging” or “enthalpic relaxation”) [36,37]. For implant applications, which perform always below T_g , in-service crystallization is not a concern. However, crystallization while heating from the glassy state greatly complicates the task of rigorously quantifying the crystallinity, even for medical grade PEEK.

The effect of processing on crystal size, thickness, and density have been studied extensively over the past two decades using idealized samples, typically films or sheets <1 mm thick, which can be thermally processed under isothermal and dynamic temperature profiles [29,30,34-36, 38-47]. Under isothermal conditions, the extent of crystallization (X) over time (t) in PEEK can be described by the Avrami relationship [34,38]:

$$X(t) = 1 - \exp(-kt^n) \quad (1)$$

where k relates the growth of nucleation in the polymer and n depends on the mechanism of nucleation. For PEEK, $n = 3$, and the k ranges over three orders of magnitude depending upon the temperature chosen for the isothermal crystallization experiment [34]. To adequately describe the competing mechanisms of nucleation and growth of crystals in PEEK under non-isothermal conditions near the melt transition, more complex models than the Avrami relationship are useful [38].

Quantification of crystalline content and microstructure for PEEK and its composites in previous studies has been determined by x-ray diffraction (e.g., wide angle and small-angle x-ray diffraction, WAXS and SAXS), scanning electron microscopy (SEM), transmission electron microscopy (TEM), gravimetric (density) analysis, differential scanning calorimetry (DSC) techniques, and/or fourier transform infrared spectroscopy (FTIR) [29-31,34,39, 41-46,48,49]. Of these methods, x-ray diffraction provides much of the foundation for density and DSC analysis, including values for the theoretical density and heat of fusion of 100% crystalline PEEK. From x-ray measurements, the density of the fully crystalline and amorphous phases of PEEK has been determined to be 1.400 and 1.265 g/cc, respectively [31]. Different values for the heat of fusion (ΔH_f) have been reported for perfectly crystalline PEEK [29], however the most widely used reference, used in many DSC analyses, is 130 J/g [29].

X-ray diffraction, density, and DSC analyses are each associated with unique drawbacks, which have prompted some discussion in the literature [41,50]. For x-ray diffraction, difficulties arise in separating out the crystalline peaks from the amorphous background [41]. For gravimetric analysis, the presence of fillers and voids can result in experimental errors [41,42]. For DSC, crystallization during the thermal analysis itself can contribute to uncertainty in both the intensity and location of the melt transition [41,50] and therefore for accurate determination of crystallinity DSC should be discarded.

Infrared spectroscopy can also be used to determine polymer crystallinity by the identification of an absorption band specific to the crystalline phase. The early reports of this technique by Cebe [51] and Chalmers [49] has been refined by Jones and Legras [52] who have shown that PEEK crystallinity can be evaluated by comparing the absorbance area ratio of the 947 cm^{-1} band to the $1,011$ or 952 cm^{-1} reference bands. Although these three methods have been widely used to examine the morphology of PEEK and its composites, the reader should be aware that such data may be subject to systematic biases, and hence must be interpreted with caution.

Each of the crystallinity evaluation techniques described above relies on the validity of a simple two-phase model, in which the properties of the amorphous and crystalline phases are totally separate. This is, of course, a simplification of physical reality for every polymer, and the literature has shown that PEEK contains rigid amorphous regions due to crystallites [53]. This is associated with a configurational entropy decrease in liquid-like interlamellar regions, leading to an increase in the glass transition temperature of these regions.

The variability of the density with crystallization temperature observed and investigated by Hay et al. [54] may be linked to the influence of the crystalline regions by the amorphous regions. The increase in crystallization temperature may result in thicker lamellae, which would have a direct effect on ability of the chain packing into crystalline lamellae.

Chemical, Thermal, and Radiation Stability: Implications for Sterilization and Post-Irradiation Aging

The structure of PEEK confers outstanding chemical resistance (Figs. 1 and 2). The aryl rings are interconnected via ketone and ether groups located at opposite ends of the ring (referred to in chemistry as the “para” position). The resonance stabilized chemical structure of PEEK results in delocalization of higher orbital electrons along the entire macromolecule, making it extremely unreactive and inherently resistant to chemical, thermal, and post-irradiation degradation. We have already noted that PEEK cannot be damaged by exposure to solvents except for concentrated sulfuric acid. The inherent inertness of PEEK's chemical structure also explains its biocompatibility, which will be more fully discussed in a subsequent section of this review.

PEEK has a water solubility of 0.5 w/w%, but as mentioned above is not chemically damaged by long-term water exposure, even at temperatures of up to 260°C [55-57]. Although PEEK itself is not susceptible to hydrolysis, concerns have been raised that interface between the polymer and reinforcements, such as carbon fiber, may be vulnerable to fluid environments *in vivo* [58]. In addition, Boinard and coworkers have found evidence that water absorption may slightly reduce the crystallinity of PEEK [57]. Consequently, it has been considered important to account for fluid exposure in biomechanical testing of PEEK composite materials for implants [5,59,60], especially if slight changes in weight are going to be used as a marker for material loss, as in a wear experiment. Water absorption in PEEK and carbon fiber composites follows an exponential relationship over time, consistent with a Type I Fickian diffusion process [57]. Presoaking specimens for 30 days has been estimated to account for 98% of fluid absorption by PEEK prior to conducting a long-term mechanical test [60]. Cyclic compression fatigue experiments conducted on carbon-fiber reinforced PEEK composites in saline at temperatures ranging between 37°C and 95°C have shown no significant change in compressive modulus, Poisson's ratio, and compressive strength after 5,000 hours of testing [60]. Several other studies have similarly observed that no significant changes occur to flexural mechanical properties in PEEK composites after exposure to high temperature saline environments [5,59].

The thermal stability of PEEK has been studied because of its high-temperature industrial applications and processing conditions. Studies have shown that thermal degradation occurs in PEEK at temperatures between the glass transition and melt transition, but that temperatures exceeding the processing temperature of PEEK are needed to produce volatile degradation products [61-65]. Hay and Kemmish reported that thermal degradation, accompanied by the generation of volatiles, was difficult to measure below 427°C [61]. Cole and Casella studied thermal degradation in PEEK and CFR-PEEK composites between 400° and 480°C using Fourier transform infrared (FTIR) spectroscopy techniques [64,65]. No significant difference was found in the thermal degradation behavior of neat PEEK as compared with CFR-PEEK composites. Buggy and Carew investigated the degradation of flexural properties and crystallinity in oriented PEEK composite laminates (APC-2) between 120°C and 310°C for up to 76 weeks [62,63]. At 120°C, below the glass transition temperature for PEEK, negligible changes in the static and fatigue properties of the composite were observed [62]. At 250°C, mechanical degradation was detected after 16 weeks of thermal aging, whereas aging at 310° C produced “rapid” degradation [62]. Based on these studies, it is clear that thermal degradation is not a concern during clinical use of PEEK biomaterials around 37°C.

Radiation stability is another common concern for aliphatic polymers, including polyolefins such as UHMWPE, which are susceptible to bond cleavage during irradiation, leading to the generation of long-lived macroradicals (often referred to as “free radicals”) [66]. In contrast, because of its distinctive aromatic chemical structure, PEEK displays remarkable resistance to gamma and electron beam radiation, with G values of radical formation about two orders of magnitude lower than aliphatic polymers, such as polyethylene [67]. Furthermore, even though free radicals are generated during irradiation of PEEK, they rapidly decay, likely due to recombination reactions made possible by the mobility of electrons along the molecular chain [68]. In studies of free radical decay using electron spin resonance (ESR), Li et al. [68] found no evidence of residual free radicals in PEEK immediately after exposure with up to 600 kGy of gamma radiation, indicating that any free radicals produced by irradiation of PEEK have a lifetime of less than 20 minutes, which was the time needed to transfer the samples from the irradiation chamber to the ESR instrument in their experiment.

The radiation stability of crystalline and amorphous PEEK has been extensively studied for the past two decades due to interest in spacecraft applications and nuclear fusion reactors, where the total exposure to radiation ranges between 10 and 50 MGy (i.e., 10,000 – 50,000 kGy) [56,67,69-77]. Although degradation and crosslinking of PEEK occur at doses above 10 MGy, it should be appreciated that the exposures of concern to the aerospace and nuclear power industry exceed the standard sterilization doses for medical devices (25-40 kGy) by three orders of magnitude. Repeated sterilization, with up to four 25-40 kGy doses of gamma radiation in air, has been confirmed to result in no significant changes to the mechanical behavior of PEEK and PEEK carbon fiber composites [59].

Therefore, published radiation stability data indicates that PEEK components may be effectively sterilized by gamma irradiation in air. Although it is possible to gamma sterilize PEEK components in a low oxygen environment, unlike UHMWPE, such advanced packaging would not be expected to confer improved shelf life. Test methods have been developed to thermally accelerate the post-irradiation degradation mechanisms of UHMWPE after gamma sterilization in air [78]. Due to its inherent thermal resistance, conducting analogous accelerated thermal aging experiments on gamma sterilized PEEK is unwarranted, because previous thermal aging temperatures used for UHMWPE (70-80°) are far below the glass transition temperature in PEEK (144°C). In summary, below the glass transition, and for doses below 600 kGy of gamma radiation, post-irradiating aging is not expected to be a clinically relevant concern with PEEK biomaterials as it has been, historically, for UHMWPE.

Mechanical Behavior

As a family of polymeric biomaterials, PEEK and its composites provide implant designers with a broad range of mechanical behaviors from which to choose. Despite early great interest in the mechanical properties of composite PEEK materials [79], it has been increasingly appreciated that the sensitivity of certain composite properties, especially fatigue and fracture behavior, is mechanistically governed by the micromechanics of the PEEK matrix and its interface with reinforcing fillers [80,81]. Like any semi-crystalline polymer, the mechanical behavior of PEEK is, generally speaking, influenced by both strain rate and temperature [57, 80,82-84]. Furthermore, the mechanical behavior of PEEK can also be influenced by molecular weight as well as the size and orientation of the crystalline regions [84-86]. As a consequence, previous studies exploring mechanical behavior of PEEK pay special attention to the resin employed (reflecting the molecular weight), temperature, strain rate, and the crystallinity of the samples employed [57,82-86].

Despite its relatively rigid molecular chain structure, virgin (unfilled) PEEK has considerable ductility and can accommodate large deformation plastic flow in both uniaxial tension and compression. Research by Hamdan and Swallowe [82] on 150G PEEK material, as well as recent investigations by Rae et al. on 450G PEEK material [84], provide comprehensive treatment of the engineering and true stress-strain behavior of PEEK. At small strains (<0.03), room-temperature PEEK displays a linear relationship between stress and strain in both tension and compression, the slope of which is characterized by an elastic modulus (Fig. 3). As the strain increases, room-temperature PEEK exhibits a clear yield transition in the slope of the stress-strain curve (Fig. 3). The yield transition in compression is 30-40% higher than in tension [84,85]. Beyond the yield transition, PEEK displays varying post-yield hardening (or softening) characteristics in tension and compression, depending upon the temperature and strain rate (Fig. 3 & 4). At large deformations in uniaxial tension, PEEK undergoes molecular alignment and localization of a neck, which complicates characterization of its true-stress strain behavior up to failure [84]. This necking artifact does not occur in uniaxial compression, and PEEK can be shown to undergo strain hardening at large deformations with true compressive strains between 1 and 1.5 [84]. In a uniaxial tension test, the local tri-axial stress state that evolves within the necked portion of the gage region limits the plastic flow of the material and contributes to rupture of the specimen at engineering strains of around 0.8 (Table 3).

When regarded in the broad context of industrial engineering applications, the mechanical properties of PEEK generally decrease with elevated temperatures up to 250°C, with a pronounced drop-off in properties above 150°C (i.e., for temperatures exceeding the glass transition temperature) [57,80,82-84]. However, within the context of biomaterial applications, where the expected operating thermal environment is around 37°C (body temperature), the elastic behavior of PEEK is relatively insensitive to temperature. The yielding, plastic flow, and fracture behavior of PEEK display greater sensitivity to test temperature below the glass transition than elastic properties (Figure 4A). Implant applications that can involve heat generation, such as impact loading during installation, or frictional contact in a joint replacement, may involve more detailed consideration of thermal effects on mechanical behavior.

As shown in Figs. 3 and 4, unless the material exceeds the elastic limit, temperature as well as strain rate should not be primary material concerns for PEEK biomaterials in clinical use. The elastic properties of PEEK are relatively unaffected by rate effects at body temperature, which is below the glass transition [82-84]. However, the yielding and plastic flow behavior is slightly affected by strain rate at physiological temperatures. In uniaxial compression, varying the strain rate by seven orders of magnitude (from 10^{-4} s^{-1} , corresponding to nearly quasistatic loading, to 10^3 s^{-1} , corresponding to impact loading) increases the yield strength by around 30% [84]. A number of interesting thermo-mechanical phenomena, including changes in crystallinity,

deformation-induced heating, macroscopic discoloration, and viscoelastic recovery-induced rupture, can all accompany high strain rate, large deformations of PEEK associated with impact [84]. The relevance of rate sensitivity should be considered when performing mechanical test evaluations of devices that may be implanted by impact loading, such as PEEK hip stems and bone anchors.

When comparing virgin PEEK materials with the same molecular weight, the elastic modulus, yield stress, and plastic flow behavior will be strongly influenced by crystallinity [85]. The crystallinity, in turn, reflects the thermal processing history of PEEK, as discussed in a previous section of this review. Injection molded parts, in which the cooling rate varies with thickness, will thus be susceptible to heterogeneous material properties, because of their spatially varying crystallinity [79]. The formation of a lower-crystallinity surface “skin” can be addressed by subsequent thermal treatments, by machining away of any amorphous skin, or by molding test specimens of sufficient thickness as to render the presence of a thin surface skin negligible [79].

Although the mechanical behavior of PEEK and its composites may be complex, previous authors have found it helpful to adopt a more simplified, descriptive perspective by grouping material properties governing the stiffness, strength, and toughness of PEEK [79,85]. Stiffness encompasses the initial elastic modulus, as well as the post-yield softening/and or hardening behavior of the material at large deformations. Strength properties include yield and ultimate stress characteristics, whereas toughness covers a broader range of fracture properties, under static, impact, and fatigue loading conditions. A recent review of toughness characteristics of PEEK, and the associated limitations with interpreting the results of these kinds of tests, has been concisely provided by Rae et al. [84].

The fatigue behavior of PEEK was first reviewed by Jones [79], who reported that the dynamic failure behavior of carbon-reinforced materials was superior to glass-reinforced and neat PEEK. The crack growth behavior of PEEK has been studied using a fracture mechanics perspective [87,88]. However, the fatigue behavior of CFR-PEEK is complex, as it involves interactions between the polymer and fiber [89]. The incorporation of laminated composite structures using long carbon fibers introduces further complexity into the structural response under dynamic loading conditions, as the fatigue strength depends upon the length as well as the orientation of the fibers relative to the loading direction [63].

Although a fundamental understanding of fatigue and fracture mechanisms in PEEK is essential from a basic science perspective, at present, the ability to apply fracture, fatigue, and impact test results to the engineering design of implants remains extremely limited. In practice, mechanical test methods are most often used by bioengineers to rank materials and composites, rather than to make decisions in implant design. An example of this practice can be found in the fatigue evaluation of bioactive PEEK materials incorporating hydroxyapatite [90]. Functional fatigue testing, in which implant components or representative samples are subjected to expected service loads, have been reported for CFR-PEEK fracture fixation plates [5] and hip stems [91].

Several mechanical properties for PEEK and selected CFR-PEEK composites are summarized in Tables 2-3. However, these summary data, while helpful for comparative purposes, should be viewed as the most basic starting point for biomaterial selection by an implant designer [79]. As we shall see, especially in the third part of this review, consideration of the biomechanical demands of particular spine, trauma, and orthopedic implants are application specific. Consequently, the development of analytical methods, as well as functional fatigue and wear testing, for PEEK biomaterials has been approached in the context of specific implant designs. In the next part of the review, we consider the scientific evidence related to the

biocompatibility of PEEK biomaterials, both from an *in vitro* perspective, and from a clinical perspective in orthopedic, spine, and trauma implants.

Biocompatibility and Bioactivity

Although, in retrospect, it might appear self evident that a widely used biomaterial is biocompatible, this topic has only been closely studied in the literature starting in the late 1980s [1]. Considerable scientific evidence currently exists to support the biocompatibility of PEEK and PEEK composites as a family of biomaterials in bulk form [1,92-98]. PEEK-OPTIMA and carbon fiber reinforced PEEK-OPTIMA compounds and composites have undergone extensive biocompatibility testing to meet the criteria for their FDA Master Files. These include numerous studies on the systemic and intracutaneous toxicity and intramuscular implantation, all of which have shown no adverse side effects. Sensitisation tests in accordance with ISO 10993-10-1995 showed no sensitisation, and gene toxicity tests showed no chromosome aberrations due to PEEK. However, concern has been raised about the inertness of PEEK and limited fixation with bone. Accordingly, increasing effort has been directed during the past decade to improving the bone-implant interface, by producing composites with hydroxyapatite, by coating PEEK implants with Ti and HA, and by creating porous PEEK networks for bone ingrowth. In this section, we review the historical literature on biocompatibility of PEEK. We also highlight recent advances in the development of bioactive PEEK composites and in the improvement of bone-implant interfaces.

Cell Culture and Animal Studies of Bulk PEEK Biomaterials

To aid in the interpretation of the literature, we have grouped studies according to whether their main emphasis lies in toxicity and/or cytotoxicity, immunogenesis, or genotoxicity. The authors are unaware of published *in vitro* studies related to carcinogenesis of PEEK. On the other hand, as summarized later in this review, the clinical experience with PEEK in humans has thus far not raised any concerns about carcinogenicity.

Toxicity/Cytotoxicity Studies—Williams and colleagues reported the first animal studies of PEEK in the literature [1]. Neat PEEK and carbon-fiber reinforced samples produced by ICI (including 450G resin) were subcutaneously implanted in rabbits for 6 months and submuscularly implanted in rats for 30 weeks. Williams stated that PEEK elicited a “minimal response” in both animal models [1].

The first cell culture cytotoxicity experiments published for PEEK were performed by Wenz et al. using mouse fibroblasts [92]. A 30% PAN carbon-fiber reinforced composite PEEK material (LNP Corporation) was evaluated. After 96h of exposure to PEEK, the cell culture was healthy and did not appear different than negative controls. The authors concluded that the PEEK composite exhibited “excellent” *in vitro* biocompatibility in this cell culture model.

The growth and attachment of osteoblasts and fibroblasts to PEEK was evaluated by Hunter et al. in a series of cell culture experiments [94]. 450G PEEK resin was employed. Ti alloy, CoCr alloy, and UHMWPE were used as controls. Cell lines were obtained from rat osteogenic sarcoma (osteoblasts); rat tail tendon (fibroblasts); and human fetal lung (fibroblasts). Although material composition had an effect on fibroblast attachment (UHMWPE had the lowest), no significant difference was noted on osteoblast attachment among the various materials evaluated. The results of this study suggested that PEEK did not appear to deleteriously affect osteoblasts and fibroblasts.

The response of osteoblasts and fibroblasts to an unknown grade of PEEK was also studied by Morrison and coworkers [95]. Fibroblast cell lines were derived from the 3T3 mouse, whereas the osteoblasts were derived from neonatal rats. The authors found that PEEK was not cytotoxic

and suggested it be considered in the development of isoelastic hip stems. Indeed, the osteoblast cell line cell protein content appeared to be stimulated by the CFR-PEEK, suggesting some stimulatory effect from the material on osteoblasts.

A similar cell culture study using osteoblast and fibroblasts was conducted using carbon-fiber reinforced PEEK [99]. The grade of PEEK employed in the study was not described. In this study, Macnair et al. [99] placed special emphasis in characterizing the surface of the PEEK composite, which was found to be significantly rougher than Ti alloy. The cellular response to PEEK composite was noted to be similar to the results from Hunter's study [94].

More recently, Scotchford *et al.* [100] examined the *in-vitro* biological response of human (trabecular bone) osteoblasts and murine macrophages to chopped CFR-PEEK polymer with a view that the material has potential as a total hip replacement. CFR-PEEK and titanium alloy (Ti6Al4V) discs showed no significant difference in the extent of osteoblast attachment and proliferation.

Human-derived osteoblast cell cultures have been used to evaluate a 10% chopped glass fiber composite PEEK [97]. In this experiment, the surface roughness of the "GPEEK" was varied between 3 and 9 μm . All of the GPEEK surfaces were found to promote proliferation and continued functioning of osteoblasts over the 5-day duration of exposure.

Additional cytotoxicity testing was performed by Katzer et al. [98] on 381G PEEK resin. Among the hundreds of test methods available to characterize such attributes, the investigators selected the hypoxanthine-guanine-phosphoribosyl-transferase test for cytotoxicity. The results of these tests confirmed that PEEK was not cytotoxic.

Immunogenesis—Petillo and coworkers studied the inflammatory response of an unspecified grade of PEEK using a cage implant system in rats [93]. This study focused on details of the early cellular response to implantation of a variety of polymeric biomaterials after 4, 7, and 14 days. The authors found evidence to support their hypothesis that polymer composition influenced the cellular response following implantation, but the clinical significance of these findings was not clear.

Jokish *et al.* [101] implanted CFR-PEEK into rabbit muscle over eight to twelve weeks and observed normal muscle tissue with no adverse tissue response and no visible infection with only a few inflammatory cells when analysed histologically. The tissue response was comparable to UHMWPE. The researchers' second phase study used CFR-PEEK as internal fixation devices for transverse midshaft femoral osteotomies in canines and demonstrated the material to be effective in promoting fracture healing with a non-specific foreign body response shown to plates and particulate debris.

Genotoxicity—Genotoxicity testing was performed by Katzer et al. [98]. The Ames test was selected to evaluate PEEK 381G resin for mutagenicity. These tests confirmed that PEEK was not mutagenic.

Summary of Cell Culture and Animal Studies—Overall, the available cell culture and animal studies spanning two decades of research strongly demonstrate that PEEK and PEEK composite biomaterials are effectively inert, biologically speaking, when these polymers are tested in the bulk state. The inertness of PEEK in a biological environment is hardly surprising in light of the chemical stability of the polymer, discussed earlier in this review. Although the biocompatibility testing of bulk materials is a necessary first step, additional research is necessary to validate the tissue response to as-manufactured implants and wear particles; these concerns are addressed in subsequent implant-related sections of this review.

Bioactive PEEK Composites

Because PEEK materials are considered to be relatively inert in a biological context, over the past decade there has been interest in further tailoring the polymer to stimulate bone apposition for load bearing orthopedic applications [22-25,90,102-106]. Bioactive PEEK composites were created by compounding the PEEK with calcium phosphate biomaterials, such as beta-tricalcium phosphate (β -TCP) and hydroxyapatite (HA). Researchers have generally chosen 450G as the PEEK resin for their composites research.

The initial research on PEEK-HA composites was concerned with characterizing the composition and thermal characteristics of the polymer mixture [103,106]. These pilot studies confirmed that HA did not interfere with the crystallization or melting processes of PEEK-HA powder mixtures. Injection molding has since been a common method reported in the literature to produce PEEK-HA composites with HA fractions of up to 40% by weight [25,90,102,104,105], although in one study researchers employed pressureless sintering to make specimens for biocompatibility testing [22]. Selective laser sintering has also been proposed as a novel method to produce three-dimensional PEEK-HA composite scaffolds for tissue engineering [24].

Subsequent research has focused on characterizing the *in vitro* bioactivity [22,105] as well as the static and fatigue mechanical behavior of PEEK-HA composites [23-25,90,102,104,105]. Although *in vitro* studies have provided encouraging results regarding the bioactivity of PEEK-HA composites, the data from mechanical characterization has been mixed. On one hand, loading PEEK with HA particles demonstrates a significant increase in elastic modulus [25,102,104,105]. However, in contrast with carbon and glass fiber additives, HA in particular, and to perhaps a lesser extent β -TCP [105], does not show a strong mechanical affinity to the PEEK matrix. Furthermore Petrovic et. al. [105] observed the viability and proliferation of normal human osteoblasts onto PEEK compounded with 5-40% β -tricalcium phosphate (β -TCP). The researchers concluded that pure PEEK was non-toxic and that cell proliferation was progressively inhibited when β -TCP was present. This suggests that PEEK possesses good biological interaction even without the addition of traditionally bioactive components as enhancements.

Scanning electron micrographs of the fracture surface of PEEK-HA composites show the HA particles completely debonded from the PEEK matrix (Fig. 5). As a result, increasing the concentration of HA in PEEK has the effect of substantially reducing the strength and toughness of the composites [25,102,104,105]. Although carbon fiber reinforcement does compromise the ductility of the composite, the loss of ductility is offset by a substantial increase in strength (Table 3). No such strength benefits have been reported for PEEK-HA composites. In contrast, loading PEEK with 40% HA has been shown to decrease the ultimate tensile strength of the material by 45%, to 44 MPa, which is comparable to cortical bone.

In summary, PEEK-HA composites show great promise as bioactive implants but may involve a trade-off in the load carrying capacity relative to other PEEK composites, especially at 40% concentration levels of HA. Detailed micromechanical analyses [23,90] would suggest that the weak link in current bioactive composites lies at the PEEK-HA interface. On the other hand, animal studies with 20% HA loaded PEEK have shown that cells will grow into the pores of the composite [25]. Although researchers have advocated PEEK-HA composites for high load orthopedic applications [25], further research is needed to either improve the adhesion of HA particles to the PEEK matrix, or to more clearly delineate which HA concentrations may be suitable for specific orthopedic applications.

Bioactive and Textured Surface Engineering of PEEK Implants

Many of the biocompatibility studies summarized previously in this review have been concerned with tissue integration of PEEK and PEEK composites. As we have seen, incorporating high levels of HA into PEEK can promote bioactivity, but can have drawbacks with regard to strength and toughness. Consequently, the study and modification of polymer interfaces, as opposed to composite engineering of the bulk biomaterial, is another active area of academic and commercial research involving PEEK. In an effort to improve the bone-implant interface, investigators have coated PEEK and PEEK composites with Ti alloy, as well as with hydroxyapatite (HA) [96,107]. Plasma deposition processing techniques are compatible with PEEK [96,108]. Surface modification of PEEK may also be employed by wet chemistry [109,110] and by plasma treatment [111,112] to improve biocompatibility.

Cook and Rust-Dawicki have investigated the bone apposition in Ti-coated CF/PEEK for dental implant applications [96]. The authors reported that the Ti coating was 2000Å thick and was created by plasma vapor deposition, but no details are provided about the PEEK composite specifications or the coating methodology. Coated and uncoated CFR-PEEK rods were implanted in dogs for up to 8 weeks and evaluated for bone apposition as well as bone-implant interface strength using push-out testing. Interestingly, the coated implants exhibited significantly greater bone apposition than the uncoated implants according to histology, but direct apposition of bone was observed for both coated and uncoated PEEK samples. However, push-out testing revealed no significant difference in interface strength between the two groups of implants.

Although some information about coating technology can be obtained from the literature [108], most of the processing details for surface engineering of PEEK implants remain proprietary. Today, commercially available PEEK orthopedic implants are produced by thermal plasma spray coating with hydroxyapatite. Alternatively, implants are also produced by plasma spraying with titanium, followed by thermal plasma coating with hydroxyapatite. The objective of dual-coating with titanium and hydroxyapatite is to assure bone with the well-proven, biocompatible implant surface (titanium) after hydroxyapatite has been absorbed *in vivo*.

Controlled surface texture, including porosity, is a desirable attribute to help assure bone-implant fixation. A variety of techniques have been employed to achieve surface texture with PEEK. One method, established for composite hip stem applications, is to injection-mold PEEK core onto a textured, three-dimensional Ti surface. Another method, currently under development, is to introduce porosity in PEEK during fabrication (Fig. 6). Using rapid prototyping techniques, porous PEEK/HA composite scaffolds have also been produced by selective laser sintering [24,113]. In summary, many avenues, ranging from bioactive bulk materials, to bioactive coatings and the development of surface texture, are currently being explored for fixation of PEEK implants in cementless applications. In the following section, we summarize the clinical applications of PEEK in spine, orthopedics, and trauma.

Clinical Applications

Starting in the mid to late 1980s, orthopedic researchers at several institutions became aware of high performance thermoplastics employed in the aerospace industry and began exploring their use in composite trauma and hip stems [4,5]. The orthopedic and biomaterials literature of the 1990s reflects this early academic curiosity, but widespread commercial applications for PEEK biomaterials in the human body would be first realized in the field of spine implants. Consequently, the early clinical history of PEEK biomaterials is more heavily weighted by the spine literature. PEEK biomaterials, in particular carbon fiber reinforced PEEK, have been explored for bearing material applications. Although the polymer continues to be clinically

investigated as an orthopedic bearing and hip stem material, PEEK biomaterials are now widely accepted in the spine field as the material of choice for fusion cages, and are currently under evaluation for more demanding spine stabilization products.

Trauma Implants

Implantable biomaterials have been used to treat fractures for over a century [114]. Internal fixation of long bone fractures using metallic plates was first reported by Lane in 1895 [115]. Difficulties with early metal implants were encountered due to corrosion [114], but these were eventually surmounted using stainless steel. In recent decades, one of the concerns about metallic fracture fixation devices has been the reduction in bone quality adjacent to the plate, due to stress shielding [114].

“Semi-rigid” carbon-fiber reinforced polymer fracture fixation plates were developed starting in the 1980s as an alternative to comparatively “rigid” stainless steel bone plates [116-121]. As a historical note, an investigation of carbon-fiber reinforced polymer fracture fixation plates was reported by Bradley et al. in the first published issue of *Biomaterials* [121]. A commercial epoxy prepreg resin was chosen as the polymer matrix for the plates, and these implants exhibited 1/3 the bending stiffness and 10% greater flexural strength than steel plates. The biocompatibility of CFR-epoxy plates was confirmed to be comparable to stainless steel plates by testing biopsy samples from tissue obtained when the devices were surgically removed following fracture healing [122]. However, an important disadvantage of a thermosetting polymer, such as epoxy, is its inability to be contoured to the bone fragments of a fracture, rendering it less clinically useful than metallic or polymeric plates that have this capability.

High performance, thermoplastic materials, including and nylon 6-10, polybutylene terephthalate (PBT), polysulphone (PS), and PEEK, were also extensively studied as candidates for fracture fixation devices [5,123]. Throughout the 1990s, researchers at Case Western contributed to the literature on the biocompatibility of PEEK, as well as composite hip stem development [5,92,101,124]. Although researchers were curious about these advanced polymers due to their mechanical performance and isoelasticity, they also hoped to take advantage of the thermoformability of the materials, so that the fracture fixation plates could be more precisely fit to patients' bony anatomy in the operating room, thereby overcoming a previous limitation of thermosetting polymers, namely epoxy.

Brown et al. [5] examined the flexural fatigue and thermoformability of PS, PBT, and PEEK reinforced by 30% chopped PAN carbon fibers. Flexural bars were subjected to a variety of challenges, including repeated steam sterilization, and presoaking for 3 weeks in saline (0.9% NaCl). Bars were also tested before and after a thermoforming procedure, which involved heating above the glass transition temperature in an oven followed by deformation in a surgical plate bending press. In the case of the PEEK composites, they were heated to 250°C and bent to an angle of 5.8°. The samples were returned to their original shape by reverse bending. The researchers found that not only did PEEK exhibit the highest fracture toughness and bending fatigue resistance of the materials studied, but that the properties were insensitive to preconditioning or thermoforming. In contrast with PBT and PS, PEEK exhibited good compatibility with the carbon fibers, which helped explain its superior fatigue resistance.

Despite the identification of CFR-PEEK as a suitable material for fracture fixation in the peer-reviewed literature as early as 1990, the use of composites for internal fracture fixation progressed as a research topic, but not a clinical research application. Over the past decade, research has continued on the development of braided, laminated, and unidirectional fiber-oriented PEEK fracture fixation plates, as well as extruded PEEK screws [125-129]. These papers describe perceived limitations in the manufacturability of the complex composites as historical barriers to the use of CFR-PEEK as fracture fixation plates.

Epoxy, but not PEEK, composite fracture fixation plates are currently commercially available (Carboxy: Orthodynamics, Ltd., Dorset, UK). According to product literature available from the manufacturer, Carboxy plates have been used to treat over 1,000 fractures since 1982. However these implants account for only a small fraction of fracture fixation devices that have been deployed clinically over the past two decades. In the United States alone, over 600,000 internal fracture fixation procedures of the femur, tibia/fibula, radius/ulna, and humerus were performed in 2004 [130].

Despite gradual changes in surgical technique and implant design, metallic locking plates and intramedullary nails continue to dominate the field of internal fracture fixation, as they have for over 100 years [114,131,132]. Because the biomechanics of fracture fixation depends upon the bending stiffness (the product of the moment of inertia and elastic modulus) of the bone-implant complex, not simply the elastic modulus of the implant, the stress shielding arguments of the 1980s are not currently regarded as credibly advantageous, because the bending stiffness of an implant can be altered by changing its moment of inertia, as well as by modifying its elastic modulus [133]. Furthermore, carbon-fiber reinforced polymer plates are still substantially more difficult to manufacture and more costly than their metallic counterparts [133].

To the authors' knowledge, there have been no clinical reports of the performance of PEEK materials as implanted fracture fixation devices. As we shall see, this finding contrasts sharply with the extensive clinical experience of PEEK in the spine.

Spinal Implants

PAEK biomaterials were introduced as spinal cages in 1990s by AcroMed (Cleveland, OH, now DePuy Spine, Raynham, MA). Cages were developed to stabilize the anterior column of the lumbar or cervical spine and facilitate fusion as a treatment for intractable back pain arising from degenerative disc disease and/or spinal instability. Due to the mechanical loading requirements for these permanent implants, the surgeons who helped develop the posterior lumbar interbody fusion (PLIF) cage, Arthur Steffee, M.D., and John Brantigan, M.D., initially conceived of a titanium device that would allow bone to grow through a columnar fenestration in the device (Personal communication, Christianson, B.). There were two perceived drawbacks with the initial proposed design, the first being the stiffness of the titanium device, which might promote stress shielding and inhibit bone growth, and the second being the radiopacity of the device, which would hinder diagnostic assessment of the bone growth. Carl McMillin, a polymer engineer at AcroMed, was familiar with high performance thermoplastics and recommended PAEKs for the cage to overcome both limitations [134]. The clinical and commercial success of this medical device, which came to be known as the Brantigan cage after its primary surgeon champion, lay the foundation for the current widespread use of PEEK in spine implants (Fig. 7).

Several high-performance thermoplastic resins were initially considered for the Brantigan cage, including PEK and PEEK (Vitrex), PEKEKK (Ultrapak, BASF Corporation), and polysulphone [134,135]. Initially both chopped and continuous carbon fiber composites were evaluated for the cage [135]. Although PEEK and PEKEKK were judged to be extremely similar in terms of their biocompatibility and suitability for spine implant applications, PEKEKK was noted to have a slightly higher glass transition temperature and higher tensile strength [134].

Starting in May 1989, PEEK and PEKEKK were evaluated in a two-year pilot clinical study of the spine cage for lumbar fusion in 26 human patients [136]. Both implant materials were consolidated into plates with continuous 68% by weight carbon fibers for reinforcement, and the cages were subsequently machined from the plates into their final form. In the PLIF

procedure, in addition to a cage or bone spacer, the spine is further stabilized by pedicle screws and axial rods or plates. In the 26 patients, the initial clinical trial evaluated 32 interbody cages (of two designs and two materials) and 31 alternative interbody fusion therapies, for a total of 63 total fusion levels. 31/32 cages survived 2-years of follow-up. Clinical results were good or excellent in 21/26 patients, and fair or poor results were traced back to problems unrelated to the cage. Because of the radiolucency of the cages, interbody fusion could be identified in 100% (31/31) of the cage levels. Brantigan's clinical study [136] marks the first implantation of carbon reinforced PEEK and PEKEKK in the human spine.

Based on the encouraging fusion results from the pilot clinical study and animal study [136, 137], a prospective, multi-center investigational device exemption (IDE) study was initiated for the FDA in November 1991 [13]. A total of 221 patients received a carbon reinforced PEKEKK cage with posterior pedicle screw fixation. The authors reported successful fusion in 176/178 (98.9%) patients who reached two-year follow-up. Five- to nine-year follow-up data for the Brantigan cage in a 360° fusion have also been reported [138].

Numerous studies have remarked upon the radiolucency of the neat and reinforced spinal implants fabricated from PEKEKK and PEEK, which have been found to greatly facilitate radiographic assessment of fusion in vivo [13,136,137]. Fig. 7B shows a representative radiograph of a solid fusion through the fenestrations of a Brantigan ALIF cage, although computed tomography (CT) generally provides a more reliable assessment of fusion than plane radiographs [139]. The compatibility of PAEK polymers with clinical diagnostic imaging has been a major driver for the widespread adoption of this polymer family for spinal applications.

Although many papers describe the use of CFR-PEEK for spine implants, the majority of implants involve the use of neat PEEK for both cervical and lumbar spinal cages [11, 140-147]. Because the use of neat PEEK for spine is a relatively recent development, the published literature is generally limited to in vitro biomechanical studies [145-147], or short-term outcomes in animal studies or human clinical trials [11,140-143]. Recent studies with PEEK cages have looked to improve or accelerate fusion performance by combining the devices with the use of hydroxylapatite [143], 40% β -tricalcium phosphate/60% hydroxylapatite [141], or rhBMP-2 on a collagen sponge [11].

Although most of the literature for PAEK biomaterials in the spine focuses on biomechanical stability or clinical outcomes such as fusion, relatively few studies provide insight into the unique limitations of the material when used in cage implants. The potential for some implant complications of PEEK cages, such as subsidence, are shared with metallic cages, and thus are not unique to the use of PEEK [148]. As with any load-bearing implant, wear and fracture are also concerns with PEEK spinal implants. Our experience with these implant-related complications is largely drawn from the Brantigan cage, because of its extensive clinical history. As of 1998, no implant-related complications of carbon-fiber cages had been reported in the literature. Tulberg described the fracture of a Brantigan cage in a case study of a failed fusion [149]. Togawa et al studied biopsy samples from radiologically successful fusions with Ti alloy or Brantigan cages [150]. Researchers noted particles of debris in biopsies from 4/5 carbon fiber cages and in 1/4 titanium cages, but no evidence of an inflammatory reaction to the particles was seen. The overall clinical significance of particulate debris and fracture is unclear for the Brantigan cage given the strong evidence of long-term successful fusion using this design, and similar findings to those in metal cages.

Nevertheless, due to the loading demands in the spine (especially in the lumbar region) and the competing design goals of strength and thin implant cross-sections to promote internal bone growth, the literature suggests that implant fracture and debris production could be considered important potential failure modes for PEEK biomaterials in the spine. Finite element analysis,

in particular, has proven to be an effective tool to evaluate the fracture risk of PEEK implant designs in the spine [147]. The effect of wear debris on the spinal cord has been investigated in a rabbit model [151]. After injecting particle loads into the spinal canal of rabbits, researchers have concluded that PEEK particles appear “harmless” to the spinal cord.

In summary PEEK biomaterials have over a decade and a half of successful clinical history in load sharing fusion applications in the spine. The continued availability, radiolucency, and biomechanical success of PEEK in these applications has stimulated interest in using the biomaterial in a variety of more demanding applications, including posterior dynamic stabilization and even total disc replacement. Senegas, for example, has published that the developers of the Wallis posterior dynamic stabilization system have converted their titanium interspinous component to PEEK [152]. The St Francis developed X-STOP also employs PEEK-OPTIMA as a spacer in a Interspinous Process Decompression System. Medtronic Sofamor Danek have launched the CD HORIZON LEGACY PEEK pedicle-based, posterior rod (Fig. 8) and Pioneer Surgical have a NUBAC PEEK-OPTIMA nucleus replacement device enrolled in an IDE study. At present, biomechanical and clinical data for PEEK in these novel and demanding spinal applications have not yet appeared in the peer-reviewed scientific literature and are eagerly anticipated by the spine implant community.

Femoral Stems

PEEK biomaterials in orthopedics are currently in a period of consideration and conservative adoption. The traditional metal, ceramic, and polymer implants currently used for total hip and knee replacement are perceived by many surgeons and patients as reasonably successful, with survival rates in the elderly population exceeding 90% at ten years [153,154]. The clinical needs for the orthopedic community, therefore, have been focused on extending the longevity of existing implants for the elderly patient population, as well as on expanding the clinical success of total joint replacements to younger and more active patients. Consequently, in orthopedics, novel implant technologies need to demonstrate sustained, long-term improved performance relative to historical alternatives [153,154]. Only within the past decade have animal studies and clinical data started gradually accumulating to demonstrate the viability of composite stems incorporating PEEK biomaterials as an alternative to monolithic metal alloys in hip stems [14,16].

Setbacks with Polymer-Metal Composites—The measured adoption of PEEK biomaterials in hip stems has been tempered by previous experience with the historical failures of isoelastic and Proplast-coated hip prostheses in the 1970s and 1980s, and, most recently, isoelastic polysulfone composite stems in the 1990s. The concept of a cementless “isoelastic” hip stem was reportedly conceived in 1967 by Robert Mathys as an alternative to the cemented metallic hip implant design developed by Sir John Charnley [155,156]. The isoelastic hip stem was intended to replicate the stiffness to the femur, to reduce stress shielding and improve implant fixation. The first isoelastic hip design, clinically implanted starting in 1973, was a composite prosthesis consisting of a polyacetal copolymer with a tapered metallic core (Factory for Surgical Instrumentation, Bettlach, Switzerland). This device was inserted without cement, and used a proximal lag screw for fixation. Loosening of this prosthesis, attributed to poor clinical technique and excessive proximal micromotion, also led to a second, and ultimately a third generation of the RM Isoelastic Cementless Hip Prosthesis (RMI) [155,156]. These subsequent generations differed in geometric design, but retained the same polyacetal copolymer fixation interface. Despite encouraging short-term clinical results [155,156], longer investigation, with an average follow-up of 42 months, revealed unacceptably high rates of mechanical loosening for the third-generation RMI prosthesis [157]. By 1988, Jakim and coworkers noted that, “the concept of isoelasticity that has attracted many surgeons has failed to fulfill original clinical expectations” [157].

In the 1970s and 1980s, surgeons also experimented with metallic, noncemented hip implants that were coated with a thin layer of Proplast, a porous polymer composite of vitreous carbon and polytetrafluorethylene [158]. The low-modulus, porous surface layer was employed in the hopes that it would promote cementless fixation [159]. Unfortunately, the polymer coating led to unacceptably high loosening rates and was ultimately abandoned in the 1990s [160], but unfortunately not before it had been implanted in hundreds of patients.

The BHC stem provides an example of a polymer composite, isoelastic hip stem that survived preclinical evaluation but resulted in unanticipated failures clinically. In 1985, Biomet (Warsaw, IN) formed BHC Laboratories, Inc., a joint venture with Hercules Inc. to produce high-performance composite orthopedic products. BHC developed a composite stem that was fabricated from laminated, carbon-fiber reinforced polysulfone and did not contain a metal core. An animal study, in which a CF/polysulfone hemiarthroplasty was implanted in 17 greyhounds, demonstrated encouraging bone remodeling around the stem and a “benign host-tissue response” [161]. The BHC stem was clinically implanted in Europe. Short-term fractures of the stem occurred at the neck-body junction, and the report of one such case was published [162].

Despite initial setbacks in the development of polymer-metal composite cementless femoral stems, the ideal of an isoelastic prosthesis has remained conceptually appealing to researchers in the orthopedic community. Several high-performance polymer composites, including PEEK, were recognized in the late 1980s as possible candidates for new isoelastic hip stem designs [4]. A variety of polymers, including polysulfones and PAEK materials were considered as candidate biomaterials during this period by the orthopedic community [4,59, 161,163]. In 1988, Skinner wrote that, “despite the lack of evidence demonstrating a clear need for a hip prosthesis with a lower modulus and stiffness, composite prosthetic hips are being intensively studied by the orthopedic implant industry” [4]. Notwithstanding its conceptual attraction, even in biomechanical engineering circles, the clinical importance of stress shielding in the early 1990s was a topic of considerable debate and uncertain significance [164]. Concern over stress shielding in femoral stems was totally eclipsed by UHMWPE wear-debris induced osteolysis as the defining orthopedic research issue of the 1990s [165].

PAEK Composite Stems—Many different composite hip stem design concepts were analyzed and tested in the 1990s, including the BHC stem discussed previously. Maharaj and Jamison investigated the creep behavior of laminated CFR-PEEK composite hip stems (APC-2, ICI) in lactated Ringer's solution for up to 120 days [166]. In a separate study, the same investigators also considered the effect of impact loading during hammered insertion of their uncemented CFR-PEEK stems [7]. Researchers have also employed numerical techniques, previously used to design composites for aerospace applications, to analyze CFR-PEEK hip stems [167-170].

Several composite hip stem designs were conceived by orthopedic manufacturers in this period of experimental and analytical discovery. The Bradley stem (Orthodynamics, Ltd., Dorset, UK) was developed in 1986 and implanted in 65 patients between 1992 and 1998, according to information available from the manufacturer. This composite design consists of a tapered metallic core, with a CFR-PEEK outer layer. The device is proximally coated with hydroxylapatite. The biocompatibility of the CFR-PEEK composite formulation used in the Bradley stem has been verified [100], but the clinical results of the implant have not yet appeared in the peer-reviewed literature. Another isoelastic femoral stem, the Physiologic Stem was also produced by Mathys Medical (Switzerland). This consisted of a titanium core sheathed in PEEK-OPTIMA and additionally coated with a titanium layer. The clinical performance of this stem has only been reported in conference proceedings.

Currently, the Epoch hip stem, developed by Zimmer, Inc. (Warsaw, IN), has the most extensive track record of composite femoral implants published in the literature, including animal studies [171,172], as well as human clinical trials [14-16]. The Epoch stem is a three-part composite consisting of a forged CoCr alloy inner core, an intermediate layer of PEKEKK resin (UltraPek: BASF Corporation), and outer bone ingrowth layer of commercially pure Ti fiber metal. Zimmer initiated a prospective, multicenter trial of the Epoch stem with 366 patients in 1994 as part of a Investigational Device Exemption (IDE) study for the Food and Drug Administration (FDA) [15]. At two years minimum follow up, all of the implants had achieved ingrowth, and dual energy x-ray absorptiometry (DEXA) scans on a subset of patients showed less bone loss than with metallic implants. A recent prospective study, performed at Case Western Reserve University, noted similar encouraging findings, but at an average follow up of 6.2 years [14]. Researchers also documented extensive bone ongrowth and ingrowth by performing histological sections of two femoral stems that had been retrieved at autopsy from patients who had died due to reasons unrelated to the hip replacement [14].

The 510(k) application for the Epoch stem was cleared by the FDA in July 2002. An updated version of the composite stem was developed using PEEK as the thermoplastic layer of the design. The PEEK version of the Epoch stem, branded the Versys Epoch Fullcoat stem, was cleared by the FDA in February 2006. The PEEK used in the Versys stem is Gatone resin (Gharda, India) (Personal communication, Brinkerhuff, H.).

In summary, the design ideal of isoelastic femoral stems, conceived in the 1960s, is now beginning to show clinical evidence of reasonably sustained fixation and reduced stress shielding when compared with traditional metallic stems. Although a variety of polymers have been evaluated for this application over the past 40 years, PEEK has proven to be the only polymer with the requisite combination of mechanical properties, biocompatibility, manufacturability, and consistent availability throughout this time period. Long-term clinical data are awaited to determine whether PEEK-composite stems will continue to provide similar extended benefits to patients undergoing total hip arthroplasty as have been observed in intermediate follow-up.

Arthroplasty Bearing Surfaces

Due to its excellent thermomechanical properties, PEEK and its composites have been subjected to intensive scrutiny as bearing materials since the 1980s for industrial and aerospace applications [173-175]. Tribological investigations for PEEK were typically conducted under dry, unidirectional sliding conditions, using a pin-on-disk or wheel-on-flat configuration. These basic studies established that the friction and wear behavior of PEEK depended not only upon the type and amount of fiber reinforcement, but also the surface roughness of the PEEK surface and the counterface, as well as temperature, sliding speed, and contact pressure. Although an extensive body of tribological literature exists for PEEK and its composites, when we restrict ourselves to conditions relevant to total joint replacement applications, only a limited number of investigations have been reported in the peer-reviewed literature [17, 176-179].

Total Hip and Knee Replacement—Starting in the 1990s, carbon-fiber reinforced PEEK (CFR-PEEK) composites were evaluated as candidate bearing materials for hip and knee replacement [17,176] and were compared with UHMWPE, which has been used for these applications since 1962 [180]. During the 1990s, gamma sterilized UHMWPE was the polymeric material of choice for total joint replacements. However, the orthopedic community was searching for alternate bearing surfaces, due to concerns about the major clinical problem of wear debris-induced osteolysis [78]. Around that time, manufacturers were also transitioning from gamma sterilization in air to alternative sterilization methods, such as gamma irradiation

in a low oxygen environment, gas plasma, or ethylene oxide, to reduce oxidation during prolonged shelf storage [181]. These distinctions are important when interpreting the literature, because the control material originally chosen as a benchmark for PEEK wear tests—gamma-air sterilized UHMWPE—is currently considered a historical reference, and has since been superseded by conventionally sterilized UHMWPE, as well as highly crosslinked UHMWPE, which exhibits substantially improved wear performance [181]. 2nd generation metal-on-metal (MOM), as well as ceramic-on-ceramic (COC), were also carefully studied in the 1990s as alternate bearings for hip arthroplasty [182]. Thus, highly crosslinked UHMWPE, MOM, and COC bearings had already emerged in clinical use during the late 1990s as alternatives to conventional UHMWPE [182], at around the same time as CFR-PEEK came to be first considered for similar applications.

As was the case prior to the introduction of composite femoral stems, attempts to modify UHMWPE in the 1970s and 1980s to improve its clinical wear performance had not proven successful [78]. A candidate replacement for UHMWPE, introduced in the 1970s, was reinforced by chopped, randomly oriented carbon-fibers and distributed under the trade name Poly II by Zimmer (Warsaw, IN). The history of this candidate material has been summarized recently [78]. Although Poly II exhibited increased yield strength relative to UHMWPE, wear testing demonstrated variable results, and short-term failures with the composite bearing material were observed clinically [183-185]. Upon revision, the periprosthetic tissues were found to be stained black from the carbon fibers used as reinforcement. Subsequent analysis of Poly II suggested that the composite material exhibited poor fatigue crack propagation resistance due to insufficient compatibility between the fiber reinforcement and the UHMWPE matrix [186]. Although PEEK has been shown in the fatigue literature to have excellent compatibility with carbon fibers [5], the prior history with carbon fiber reinforced UHMWPE called for a conservative tribological evaluation program for PEEK and its composites.

The biotribology of PEEK was first reported by researchers from Howmedica (Rutherford, NJ), who were aware of not only the previous industrial wear testing of composite PEEK, but also the poor clinical performance of Poly II [176]. Hip cups for wear testing were initially produced by injection molding 30% discontinuous, pitch carbon fiber (Amoco, Grade VMX-12) reinforced 150G PEEK resin. The System 12 acetabular liners had a 28 mm inner diameter and were tested in Vitallium (CoCr alloy) metal shells. Gamma air sterilized UHMWPE liners (with a nominal dose of approximately 25 kGy) were evaluated as controls. Zirconia heads (Prozyr: Desmarquest, France) were used as the counterface. Five composite cups and three controls were tested in an MTS hip simulator to 10 million cycles, representing approximately one decade of use for a typical elderly patient. Bovine calf serum was used as the lubricant. Under these conditions, the CFR-PEEK exhibited two orders of magnitude less wear than the control (0.39 ± 0.09 vs. 35.4 ± 5.4 mm³/Mcycles, for the composite and control, respectively). The authors attributed the “exceptional” wear performance of zirconia against CFR-PEEK in the hip simulator to the effective load transfer and interfacial strength of the PEEK and carbon fibers [176].

Wang et al. [17] carried out a more comprehensive tribological investigation of PEEK composites for both hip and knee bearing applications. CFR-PEEK formulations were injection molded using 150G resin blended with 20-30 w/w% discontinuous PAN or pitch fibers. The polymers were tested against CoCr alloy, zirconia, and alumina ceramic counterfaces. The suitability for hip applications was tested using the MTS hip simulator, whereas the suitability for knee applications was evaluated using a multi-directional cylinder on flat wear tester. Testing was performed up to 5 million cycles and in bovine calf serum as lubricant. Once again, UHMWPE sterilized with 25 kGy of gamma radiation in air was used as a control. Under the higher stress, cylinder-on-flat loading condition, the PEEK composites exhibited higher wear rates than the historical control (Fig. 9A). In contrast, under the lower-stress hip simulator test

conditions, all of the PEEK composites had substantially lower wear rates than the historical control, with the lowest wear observed between 30% pitch CFR-PEEK against zirconia (Fig. 9B). In contrast, unreinforced PEEK wore at 6 times the rate of the control UHMWPE. The results of this study underscored the importance of fiber reinforcement on lower stress, conforming contact applications and provided further basis for exploring the composite PEEK materials for total hip replacements, especially in combination with ceramic as opposed to CoCr heads. On the other hand, this study also suggested that PEEK composites were unsuitable for knee applications, regardless of the fiber content of the composite or the type of counterface. The authors recommended that “the composite materials should not be used as a tibial component for a total knee replacement.”

Although CFR-PEEK has superior wear performance than neat PEEK, the type of fibers has also been shown to play a role in the tribological behavior of the composite [17,187]. In unlubricated pin-on-disc studies against steel, the tribological performance of pitch vs. PAN fibers depends upon the contact pressure and sliding speed [187]. In the hip simulator studies by Wang et al. [17], composites produced by blending pitch fiber yielded lower wear rates than with PAN fibers, which were stiffer and, hence, more abrasive. Recent pin-on-disc studies of CFR-PEEK pins on alumina and ceramic composite plates have demonstrated comparably low wear rates using both PAN and pitch-fiber reinforcement [188].

In 2001, St. Gobain Demarquest suspended its international sales of zirconia ceramics from implant applications and withdrew from the market [189]. Due to an unforeseen manufacturing change, certain batches of zirconia femoral heads experienced unacceptably high fracture rates [189]. Consequently, in more recent PEEK tribology studies, zirconia is no longer considered a candidate bearing surface, even though it was initially found to be an “optimal” choice in combination with PEEK in early hip simulator experiments. Following the withdrawal of zirconia, alumina became the femoral head material of choice for THA applications with CFR-PEEK. CoCr heads, when used in conjunction with CFR-PEEK liners, exhibited substantially higher wear, with observations of scratching of the metallic surface by the carbon fibers [17].

Careful consideration has been given to the bioactivity of wear particles that may be produced from articulation. As part of a larger study on composite candidate biomaterials, Howling and coworkers [177] investigated the bioactivity of wear debris generated by a 30% PAN CFR-PEEK composite pins articulating against alumina plates in a bidirectional pin-on-disk tester. The wear particles were extracted from the test fluid and exposed to L929 and U937 cells in an *in vitro* culture model to evaluate their effect on cellular viability. The PEEK composite wear debris had no cytotoxic effects on either types of cells *in vitro*.

To validate the *in vivo* wear behavior and compatibility of CFR-PEEK wear debris, a clinical study was initiated in Italy starting in April 2001 using the ABG II total hip system (Stryker SA, Montreux, Switzerland). The ABG liners were fabricated from injection molded PEEK blended with 30% pitch fibers, and the bearing surfaces were machined to achieve the desired final tolerance. The status of the ABG CFR-PEEK trial has been reported in conference abstracts [190]. 30 patients (40%F) with a mean age of 65 years were initially enrolled in the study. After a mean follow-up of 3 years, none of the liners had been revised due to aseptic loosening [191]. Osteolysis was observed in two femurs, at the greater trochanter. Retrieval analysis of one liner, retrieved due to infection from a 55y highly active male patient, revealed head penetration of 0.13 mm after 28 months [192]. Histology demonstrated a “low” amount of particles in the periprosthetic tissue from this patient. The ABG CFR-PEEK trial was later expanded to include 121 patients by 2003. According to the manufacturer, five revisions have occurred to date, due to reasons unrelated to the bearing (infection, loosening, and periprosthetic fracture). This clinical trial is still ongoing, and the detailed results have not yet appeared in a journal publication.

Overall, the available preliminary clinical data supports the short-term effectiveness of CFR-PEEK as a bearing material for total hip replacement. However, in a traditional total hip replacement design, current data does not yet demonstrate a long-term clinical advantage of CFR-PEEK over other well-established bearing alternatives, such as highly crosslinked UHMWPE, MOM, or COC. Although initial hip simulator data illustrates the superiority of CFR-PEEK as compared to historical gamma-air sterilized UHMWPE, highly crosslinked formulations of UHMWPE have also demonstrated order-of-magnitude improvement in wear as compared to historical controls. Nevertheless, the successful, albeit short-term, ABG experience with CFR-PEEK provides the necessary basis for considering the composite in more novel, non-traditional joint replacement designs, such as hip resurfacing.

Hip Resurfacing—Hip resurfacing has emerged in the past decade as an alternate treatment for degenerative arthritis for the young active patient population. First generation hip resurfacing designs employed a large-diameter, metal-on-metal articulation, combined with a minimally invasive femoral head prosthesis and a short, cemented stabilization pin. Due to longstanding concerns about metal hypersensitivity and long-term exposure to metal ions by young patient candidates for this procedure, there is great interest in 2nd-generation hip resurfacing designs that do not employ a MOM bearing couple.

Contemporary acetabular components are hemispherical, resulting in nonphysiologic stress distributions in the acetabulum [193]. A novel horseshoe-shaped acetabular component was developed by Mr. Richard Field and Neil Rushton at Cambridge University (Cambridge, UK) with the rationale of duplicating the physiologic load distribution in the natural acetabulum, thereby reducing stress shielding, which can compromise fixation and facilitate wear debris migration into the periprosthetic bone [193-196]. The acetabular component was fabricated with an outer shell of carbon fiber-reinforced PBT and an inner liner of UHMWPE. The Cambridge cup was implanted by Field and Rushton in 50 elderly female patients. 24/50 implants were coated with hydroxyapatite, the remaining 26/50 cups were uncoated. The HA-coated implants did not exhibit significant wear or migration, but the uncoated implants migrated and 3/26 had to be revised at two years [194]. In a DEXA study of Cambridge cup patients, after two years researchers did not find a significant decrease in periprosthetic bone mineral density, as compared with unimplanted controls [195]. Consequently, the flexible, horseshoe shaped cup design appeared to afford reduced stress shielding in clinical use, as anticipated by the surgeon designers.

Based on the encouraging clinical history of the Cambridge Cup, a new flexible horseshoe-shaped, CFR-PEEK cup design was recently developed for hip resurfacing applications (MITCH: Stryker SA, Montreux, Switzerland). The MITCH horseshoe cup is injection molded using a similar formulation as in the ABG clinical trial: 30% pitch fibers blended with PEEK-OPTIMA LT3 resin. To accommodate the large ceramic head sizes associated with a resurfacing arthroplasty, the total thickness of the composite acetabular component is approximately 2 mm, which is far below the 6 mm minimum thickness of UHMWPE currently used in traditional hip replacements [197]. COC and MOM bearings, while satisfying the wear resistance requirements for a resurfacing arthroplasty, are not sufficiently flexible to be incorporated into a horseshoe shaped cup design.

The back surface of the MITCH cup has fins for initial stability. For bone apposition and long-term stability, the back surface of the CFR-PEEK cup is also initially plasma sprayed with Ti, and then plasma sprayed a second time with a layer of hydroxyapatite. This dual-layer Ti/HA coating combination is compatible with PEEK, and also has a successful clinical track record in achieving stable long-term fixation in traditional acetabular components [198].

The MITCH cup has been tested in a hip simulator under conditions comparable to previous PEEK acetabular components. After 25 million cycles, the total extent of wear for the MITCH cup ranged between 12 and 30 mm³, corresponding to an average wear rate of <1 mm³/Mcycles. Finite element analysis of the MITCH cup demonstrated that the stress distribution in the acetabulum was comparable to the Cambridge cup [20].

In summary, the MITCH cup illustrates how CFR-PEEK can help overcome the historical wear and biomechanical constraints of contemporary bearing materials for a novel arthroplasty design. It remains to be seen whether the clinical findings previously observed with the Cambridge Cup will also occur with the MITCH. Following preclinical validation, a staged clinical trial has been initiated by Field and Rushton in the UK. The first implantations were performed in February 2007. Pending the successful short-term outcome of these initial implantations, the clinical trial may be expanded into an international multi-center study.

Other Total Joint Replacement Applications—PEEK has been considered for other niche total joint replacement products, including finger joint replacements and total disc replacement. Mathys AG (Bettlach, Switzerland) currently offers an all-PEEK, two-part metacarpophalangeal finger joint. This involves an image contrast grade of PEEK-OPTIMA with a thin titanium coating. No data relating to PEEK on PEEK wear for this design has been published in the open literature.

Joyce et al. have also studied the metacarpophalangeal wear behavior of neat, unfilled PEEK and UHMWPE caps against titanium in a finger joint simulator [19]. No details about the PEEK or UHMWPE resins or sterilization conditions were reported. The UHMWPE components exhibited undetectable wear, whilst PEEK components had a reported wear rate of 0.26 mm³/Mcycles, although varied lubricant uptake in control samples prevented an accurate determination of wear. The inferior wear performance of virgin PEEK relative to UHMWPE was attributed to the lack of fiber reinforcement, and was consistent with the Wang and coworkers' previous observations of neat PEEK vs. historical UHMWPE in a hip simulator [17].

A summary of preclinical mechanical testing for a PEEK-on-PEEK lumbar artificial disc has recently been reported [199]. The NUBAC intradiscal arthroplasty device (Pioneer Surgical Technology, Marquette, MI) consists of a semi-constrained ball-and-socket joint, and is manufactured from PEEK-OPTIMA LT1. The design has been tested under a number of wear conditions including flexion/extension followed immediately by lateral bending. The wear was also assessed in accordance with ISO/DIS 18192-1, but the loading was adjusted to account for the load sharing between the annulus and the nucleus in the lumbar spine. This resulted in a wear rate of 0.39 ± 0.03 mm³/million cycles. However the most interesting aspect of the testing involved shifting the frequency to provide a non-repetitive motion where the load vector is applied over the entire load area, resulting in a wear rate of 0.45 ± 0.01 mm³/million cycles. The NUBAC device is currently enrolled in an IDE study [199].

Summary and Conclusions

The widespread adoption of a new biomaterial is necessarily a slow and careful process. The history of how PEEK biomaterials came to be increasingly accepted for spine and orthopedic implants over other high-performance thermoplastics can best be described in Darwinian terms, furthered as it was by the gradual extinction of industrial alternatives, such as Ultrapex, or by short-term failures in the clinic, as was the case with polysulfone. As has been pointed out in previous reviews, the adoption of PEEK biomaterials has been facilitated in recent years by a stable commercial supply tailored for the medical device industry and supported by the process controls and certifications that are increasingly necessary in today's stringent regulatory

environment. Although long term implant approved PEEK is currently only offered by one international producer, growing demand for these materials has stimulated great interest in PEEK biomaterial development, especially in the area of bioactive composites.

In an effort to stimulate additional biomaterial development, we have summarized the extensive polymer science literature as it relates to structure, mechanical properties, and chemical resistance of PAEK biomaterials. With this foundation, one can more readily appreciate why this family of polymers will be inherently strong, inert, and biocompatible, from the point of view that neither the bulk material nor its particulates are expected to elicit a substantially more adverse biological response than other historical biomaterials that have been in clinical use for many decades. Due to its relative inertness, PEEK biomaterials may be an attractive platform upon which to further develop novel bioactive materials, and some steps have already been taken in that direction, with the blending of HA and TCP into sintered PEEK. However, to date, HA and TCP-PEEK composites have involved a trade-off in mechanical properties in exchange for their increased bioactivity. As a result, bioactive PEEK implants are instead currently produced using plasma spray coating technology, or by injection molding a PEEK substrate onto a porous metal interface.

Thus far, PEEK has had the greatest clinical impact in the field of spine implant design, and PEEK is now broadly accepted as a radiolucent alternative to metallic biomaterials in the spine community. For more mature fields, such as total joint replacements and fracture fixation implants, radiolucency is an attractive but not necessarily critical material feature. It is only with the challenges of new designs, such as with isoelastic stems and hip resurfacing, that PEEK biomaterials can offer an attractive opportunity. Although new PEEK stem and hip resurfacing designs are encouraging and in various stages of clinical adoption, it will still be many years, perhaps a decade or more, before these novel approaches can be judged superior to their successful historical predecessors. In the field of spine implants, on the other hand, limited long-term surgical options are currently available to treat chronic debilitating back pain. For these reasons, although we would expect PEEK biomaterials to proliferate in medical devices, PEEK will continue to provide greater opportunities in the design of spine implants.

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Figure 1. Chemical formula of poly(aryl-ether-ether-ketone), commonly abbreviated as PEEK, and poly(aryl-ether-ketone-ether-ketone-ketone), commonly abbreviated as PEKEKK. Image provided courtesy of Exponent, Inc.

Figure 2. (A) Chain conformation of PEEK; (B) Orthorhombic crystal unit cell for PEEK. Image provided courtesy of Exponent, Inc.

a

b

Figure 3. Effect of strain rate on the stress-strain curves at 23°C in (A) uniaxial tension and (B) compression of 450G PEEK (Vitrex, Manchester UK), as reported by Rae et al. [84]. Reproduced with permission from Elsevier.

a

b

Figure 4.

Effect of temperature on the 450G PEEK stress-strain curves in (A) uniaxial tension (rate = $1.7 \times 10^{-4} \text{ s}^{-1}$) and (B) compression (rate = $1 \times 10^{-3} \text{ s}^{-1}$) as reported by Rae et al. [84]. Reproduced with permission from Elsevier.

Figure 5. Scanning electron micrograph of the fracture surface of a PEEK-10% HA composite. Note complete debonding of the HA particles from the PEEK matrix. Reproduced from [90] with permission from Elsevier.

Figure 6.
Example of bioactive surface engineering in PEEK implants: Developmental stage, three-dimensional porous PEEK material, image courtesy of Invibio.

a

b

Figure 7. (A) CF-PEEK Brantigan spine fusion cage, image provided courtesy of Invibio; (B) Lateral radiograph of a Brantigan cage with a solid fusion, image provided courtesy of Depuy Spine. Note that the Brantigan cage has tantalum microspheres for visualization on radiographs.

Figure 8.
Posterior dynamic stabilization of the spine using PEEK rods, image provided courtesy of Medtronic Sofamor Danek.

a

b

Figure 9.

(A) Wear performance of PEEK composites and historical, gamma-air sterilized UHMWPE in a cylinder-on-flat (knee-like) wear simulator; (B) Wear performance of PEEK composites and historical, gamma-air sterilized UHMWPE materials in a hip simulator. Image provided courtesy of Exponent, Inc., adapted from [17].

Table 1**Summary of PAEK Materials Related to Implant Use**

Polymer	Trade Name	Producer	Comments
PEEK	OPTIMA (Biomaterial)	Invibio (Subsidiary of Vitrex) Thornton- Cleveleys, UK	Manufacturer and Supplier of Long Term Implantable PEEK in CE and FDA approved devices since 1998.
PEEK	Vitrex	Vitrex, Thornton- Cleveleys, UK	Provides PEEK for blood/tissue contact less than 24 hours.
PEEK	Gatone	Gharda, India	No record of supplier implantation studies. Discontinued for medical use when acquired by Solvay in December 2005
PEEK	Keto-Spire	Solvay Advanced Polymers, LLC	Not available for implant use.
PEKK	PEKK	DuPont (Wilmington, DE)	Discontinued for medical use by DuPont
PEKK	OXPEKK	Oxford Performance Material (Enfield, CT)	Implantable Grade available.
PEKEKK	Ultrapek	BASF, United States	Discontinued in December 1995

Table 2
Contemporary and Historical Nomenclature for Medical Grades of PEEK

Property	General Purpose Grade	Medium Flow Grade	Easy Flow Grade
Historical Victrex Nomenclature	450	381	150
Invibio Nomenclature	OPTIMA LT1	OPTIMA LT2	OPTIMA LT3
Melt Flow Index	3.4	4.5	36.4
Molecular Weight (M_n)	115,000	108,000	83,000

LT1 Standard Grade

LT2 Optimised grade for melt strength and melt viscosity – recommended for tubing

LT3 High flow grade for injection moulding thin walled parts

Table 3
Typical Average Physical Properties of PEEK and CFR-PEEK structural composite biomaterials, compared with UHMWPE and PMMA

Property (ISO)	Selected In vivo PEEK Biomaterials (OPTIMA LTI)			UHMWPE	PMMA
	Unfilled (OPTIMA LTI)	30% (w/w) Chopped Carbon Fiber Reinforced (LTICA30)	68% (v/v) Continuous Carbon Fiber Reinforced (Endolign)		
Polymer Type	Semi-crystalline			Semi-crystalline	Amorphous
Molecular Weight (10^6 g/mole)	0.08-0.12	0.08-0.12	0.08-0.12	2-6	0.1-0.8
Poisson's ratio	0.36	0.40	0.38	0.46	0.35
Specific gravity	1.3	1.4	1.6	0.932-0.945	1.180-1.246
Flexural Modulus (GPa)	4	20	135	0.8-1.6	1.5-4.1
Tensile Strength (MPa)	93	170	>2000	39-48	24-49
Tensile elongation (%)	30-40	1-2	1	350-525	1-2
Degree of crystallinity (%)	30-35	30-35	30-35	39-75	Noncrystalline

Testing conducted at 23°C.