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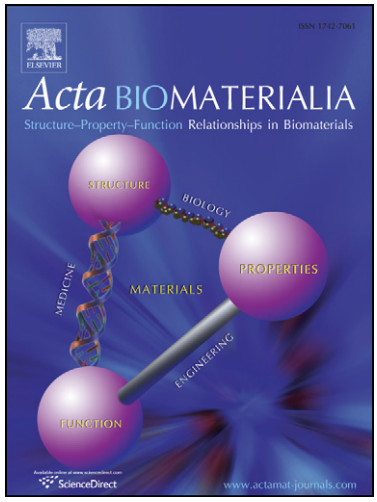

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Theoretical risk assessment of magnesium alloys as degradable biomedical implants

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Abstract

The theoretical tolerable implant masses for ten magnesium alloys as degradable biomedical implant materials were evaluated in this article. Dose-response assessment was conducted by utilizing toxicological data from authoritative public health agencies such as US Agency for Toxic Substances and Disease Registry and USEPA Integrated Risk Information System, and assuming 1 year of even corrosion. Uncertainty factors adopted by the agencies were utilized. The tolerable limits corresponding to various component elements in an alloy were separately considered, and the lowest tolerable limit was selected as the tolerable limit of the alloy. The result showed that aluminum was usually the component element with the lowest tolerance, and the tolerable mass for Al-containing magnesium alloys fall around or below 1 gram per person per year, while the limit for other magnesium alloys can well exceed 10 grams. Deficits on toxicological data of some component elements were however noted. This article illustrated that toxicological calculations should be taken into consideration when developing novel degradable metallic implants.

Keywords: aluminum; toxicology; risk assessment; metallic implant; degradable

Introduction

The research on degradable magnesium alloys (and its synonyms) as implant materials had started in 1900s-1920s[1, 2]. However, since the development of bio-stable metallic implants had matured, the investigation of bio-corrodible metallic implants had become unpopular[3]. Renewed interest of degradable / resorbable metallic implants had recently emerged in the fields of bone fixation device, cardiovascular stent and tissue engineering scaffold[3-9].

Magnesium is itself considered relatively safe[3], however the alloying elements such as aluminum, zinc and manganese are well-known to carry substantial toxicological concerns[10-12]. There appears increased evidence suggesting that Al is a risk factor for Alzheimer's disease[13-15] despite oppositions were not lacking[11, 16], but even so it is still unsure whether Al would be the sole factor[13]. Toxicological limit of this element was already developed based on its neurotoxicity, which should logically occur at lower dose than Alzheimer's disease which is a more severe form of neurological disorder. Mn is also found to affect the nervous system[12, 17]. Unfortunately, it appeared to be a trend that journals on biomaterials tend to focus on the structure, properties and functions[18].

Toxicological risk assessment is a gold standard adopted by most public health agencies, governments and institutions all over the world on assessing the risk of exposure for various potentially harmful biological or chemical substances to humans[10-12, 19-34], yet to date we could not identify any attempt made by other current researchers on the quantitative toxicological risk of magnesium alloys as a biomedical implant. For an assessment of implants intended for human application, NOAEL is more appropriate than LD_{50}, as the latter utilizes lethality as the end point thereby ignoring non-lethal health effects occurring at much lower exposure levels. Current animal studies focused on localized biocompatibility around the implant site[9, 35, 36] and did not specifically target on other potential toxicological effects that could occur, probably after a longer duration than the experiments. Without proper toxicological assessment on systemic effects, it would be impossible for any novel biomedical implant to obtain regulatory approval in a developed country, and the loss of investment could be tremendous. As a result, during an early stage of implant development, it is important to ensure that an implant composition should not pose significant health risk to human, at least theoretically, when used at a mass typical for an intended application.

Therefore, we have conducted a theoretical risk assessment to compute the lowest mass

of implant sufficient to result in any adverse side effect in some human. The toxicological issues of common alloying elements in ten standard magnesium alloys were considered based on the toxicological data from authoritative public health agencies, and the impact of the results were discussed.

This article aims to remind researchers on degradable metallic implants on the potential systemic toxicological risk of this class of implant (or any new class of biomaterial), and to attract attention of toxicologists on this matter. The focus of the current risk assessment is the threshold implant mass, which reflects the theoretical maximum mass of such biomaterial that might be safely implanted into a patient; while a judgment on the relative severity of specific adverse effects is outside the scope of this article.

Methodology

Toxicological information on critical studies of oral exposure limits were obtained from authoritative public health agencies: Agency for Toxic Substances and Disease Registry (ATSDR) of the US Department of Health and Human Services, Integrated Risk Information System (IRIS) of the US Environmental Protection Agency (EPA), and UK Food Standards Agency (FSA). The NOAEL (No Observed Adverse Effect Level)

approach for dose-response assessment was adopted[37]. Intermediate-term NOAEL was adopted whenever available. The uncertainty factors (UFs) assigned by the toxicologists in the agencies to address for the interspecies and inter-individual differences (human variability) would continue to be adopted, unless there were strong reasons for the opposition. In general, the UFs were derived in concordance with WHO guideline[37]. ASTM upper abundance limits were adopted as the abundance of component elements inside the alloys[38-40]. Gastrointestinal absorption efficiencies were obtained from ATSDR and FSA in order to adjust the exposure limits to account for an assumed 100% absorption. 60kg body weight and 365 days of even corrosion were arbitrarily chosen to represent a normal person and a degradation period reasonable for common applications.

Relevant computations were expressed by the following equations:

Equation 1

Raw Tolerable Exposure of a specific element (TE-r) for human, in mg/kg/day

= (NOAEL equivalent [in mg/kg/day]) / (interspecies UF) / (interindividual UF)

Equation 2

Absorption-adjusted Tolerable Exposure (TE-aa) of a specific element

= TE-r x absorption efficiency from oral route

Equation 3

Reference annual exposure (RAE) of a specific element for a 60kg adult (in mg/yr)

= TE-aa x 60 x 365 = 21900 x TE-aa

To determine the reference annual exposure of an alloy, the element-specific RAE of each element in an alloy was then divided by its maximum abundance in the alloy. The resultant reference value, now defined as Abundance-Adjusted Reference Annual Exposure (AARAE), would be equal to the component-specific threshold alloy mass when this component element was assumed the sole source of adverse effects.

Equation 4

Abundance-Adjusted Reference Annual Exposure (AARAE)

= RAE / abundance of the specific component element

The lowest AARAE among component elements for a given alloy would then indicate the lowest alloy mass sufficient to produce an adverse effect, as an implant to be completely

absorbed in 12 months.

Equations 1 to 4 may also be rearranged into a combined equation:

Equation 5 (combined equation)

$$\text{Threshold implant mass} = \frac{\text{(NOAEL equivalent) x oral absorption efficiency x 365 x 60}}{\text{UF x abundance}}$$

The threshold implant masses based on different component elements in an alloy were calculated individually, and the lowest value was selected as the toxicological critical value of the alloy.

Results

Literature data for the toxicological critical values of common elements in magnesium alloys and the corresponding toxicological effects are listed in Table 1, upper abundance limits of component elements in the magnesium alloys listed in Table 2, and the derived toxicological data for ten magnesium alloys are listed in Table 3.

	Al	Mn	Zn	Cu	Ni	Fe	Sr	Zr	Ce[#]
Source	ATSDR[11]	IRIS[17]	ATSDR[10]	ATSDR[24]	ATSDR[25] & IRIS[25]	UK FSA[28]	ATSDR[23]	not found in FSA/ ATSDR/ IRIS	IRIS[41]
Type of exposure limit*	NOAEL-a	NOAEL-h / RfD	NOAEL-h	NOAEL-h	EPA RfD	Guidance level	NOAEL-a	Insufficient data	Insufficient data
Potential adverse systemic effects at initial overdose**	Neuro-toxicity	CNS Effects	Reduced erythrocyte superoxide dismutase level	Changes in blood protein and enzyme levels	Reduced body & organ mass	Reduction in serum zinc; possible increased risks of cardio-vascular disease & cancer	Abnormal bone mineral-ization	Allergic hyper-sensitivity, dialysis osteo-malacia accumulates in the brain similar to Al[42, 43],	Cardiac toxicity and reduction of hemo-globin oxygen affinity
Exposure limit (mg/kg bw/day)	26	0.14	0.83	0.042	0.02	0.28	140	n/a	n/a
UF for interspecies variation	10	1	1	1	1	1	10	n/a	n/a
UF for interindividual variation	10	1	3	3	1	1	3	n/a	n/a
Oral absorption efficiency	*0.63%*	*5%*	*20%*	*36%*	*27%*	*15%*	*20%*	n/a	n/a
Modifying factor for 100% absorption (= 1 / oral bioavailability)	158.7	20	5	2.78	3.703	6.6	5	n/a	n/a
UF/absorption adjusted exposure limit (mg/kg bw/day)	1.64E-03	7.00E-03	5.53E-02	5.04E-03	5.40E-03	4.24E-02	9.33E-01	n/a	n/a
Daily exposure limit for a 60kg adult (mg/day)	9.83E-02	4.20E-01	3.32E+00	3.02E-01	3.24E-01	2.55E+00	5.60E+01	n/a	n/a
Annual exposure limit for a 60kg adult (mg/yr)	35.88	153.30	1211.80	110.29	118.28	929.09	20440	n/a	n/a

* *-h: human data -a: animal data NOAEL: No Observed Adverse Effect Level*

RfD: Reference Dose n/a: *not available*

** *inhalational and gastrointestinal effects excluded*

data deficit for rare earth metals; cerium was the sole one identified from the database, and only listed as an example

Table 1: Toxicological critical values and derived toxicological critical values for common alloying elements in magnesium alloys

	Al	Mn	Zn	Cu	Ni	Fe	Sr	Zr	Rare earth metals	Mg
AZ91D	9.7	0.5	1							
AZ31B	3.5	1	1.4	0.05	0.005	0.005				
AM60B	6.5	0.6	0.22							
AM50A	5.4	0.6	0.22							
AJ52A	5.5	0.6	0.22				2.3			
ZK61A			6.5	0.1	0.01			1		
EZ33A			3.1	0.1	0.01			1	4	
WE54A		0.03	0.2	0.03	0.005			1	4	
WE43A		0.15	0.2	0.03	0.005	0.01		1	4.4	
K1A								1		99.6

Table 2: Upper abundance limits of component elements in the magnesium alloys[38-40]

	Al	Mn	Zn	Cu	Ni	Fe	Sr	Zr	Rare earth metals	Lowest value
AZ91D	0.37	31	121					n/a	n/a	0.37
AZ31B	1.03	15	87	221	2366	18582		n/a	n/a	1.03
AM60B	0.55	26	551					n/a	n/a	0.55
AM50A	0.66	26	551					n/a	n/a	0.66
AJ52A	0.65	26	551				889	n/a	n/a	0.65
ZK61A			19	110	1183			n/a	n/a	19
EZ33A			39	110	1183			n/a	n/a	39
WE54A		511	606	368	2366			n/a	n/a	368
WE43A		102	606	368	2366	9291		n/a	n/a	102
K1A								n/a	n/a	n/a

Note: For guidance purpose, the tolerable daily intake of Mg was set at 350-400mg/day[28, 44] with bioavailability of about 50%[28], translating into 64-73g/year

Table 3: Threshold implant mass (g/year) based on different component elements in magnesium alloys

Discussion

It can be observed from Table 3 that Al-containing magnesium alloys bear tolerable masses much less than the other alloys. Not only because of the higher abundance of aluminum relative to other alloying elements in the alloys, but also because of the low element-specific annual exposure of Al. As the threshold implant mass for Al-containing Mg alloys lie between 0.37 to 1.03 grams per year, the data suggested that these alloys should pose no significant health risk to humans for small application such as cardiovascular stents, or as degradable screws (used in small numbers), but the use as multiple bone plates and screws in a patient with multiple fractures would necessitate added caution. A utilization of lower abundance limits of Al would yield similar results, as they were only 13-29% lower than the upper abundance[38-40].

While it might appear to engineering researchers that the tolerance for Al is low because an uncertainty factor of 10 x 10 = 100 was utilized, it must be noted that safety would always be the primary concern to any biomedical implant, and the uncertainty factor was specifically adopted: 10 for extrapolation of animal data to human and 10 to account for interindividual variability; therefore well-justified on a public health perspective[11, 37]. Any loosening of the standard practice could leave vulnerable patients at risk.

It may also be observed from Table 1 that no authoritative NOAEL or similar values were identified for some of the alloying elements, such as rare earth metals or zirconium. This should however be considered as a lack of sufficient information only, and it would be conceptually wrong to consider that something is safe "because of" an insufficiency of data resulted from experimental deficiencies. For example, as in the case of cerium (a rare earth metal), "an RfD for cerium was not derived because the available studies were not suitable for quantitation of effects for various reasons…" according to IRIS[41].

A report by TERA in 1999[45] had suggested oral RfDs for soluble chlorides of three rare earth elements, at 0.004mg/kg/day to 0.03mg/kg/day based on decreased body weight; however the confidence of the oral RfDs in this report was "medium to low" (original wording, page 23), and the lack of reviewed data on gastrointestinal absorption of individual rare earth metals disallowed an extrapolation of toxicological data to a 100% absorption scenario. Moreover, a decrease in body weight could probably result from gastrointestinal effects, thus this end point might not be applicable for assessing a degradable metallic implant. Despite an insufficiency of data, the report also summarized systemic toxicological symptoms identified by Haley *et al.*[46-50], such as respiratory

paralysis and impaired locomotion caused by acute intraperitoneal exposure of common rare earth metals, and perinuclear vacuolization of liver cells caused by sub-chronic oral exposure. Adverse effects of rare earth metals[51, 52] and zirconium[42, 43] were also well-documented in other articles and their references. The derived tolerable mass for ZK61A, EZ33A, WE54A, WE43A and K1A, which carry Zr and RE metals, should therefore be considered as for reference only; being data-deficient instead of carrying exceptionally low toxicity.

As for any theoretical or experimental assessment, it should also be noted that this model carries some limitations. For example, the oral and potentially inhalational intake of the metals from daily activities, which could be considerable for some elements[10-12, 17, 24, 25, 28, 53], were not taken into account. Logically, when such intake occurs, the tolerable mass should be reduced. This factor might be offset when the degradation time is increased, to the limit that the period does not exceed three years as specified by ASTM[54] for a degradable implant.

On the other hand, this model could potentially overcast the systemic toxicological concern if the corrosion products of the metals could not dissolve well in the body. Under

this condition, however, the existence of such undissolved foreign material particles or accumulated ions would create remaining symptoms[55], foreign body response[56, 57] or other localized effects that could require surgical interventions, and in such case it would be arguable for whether it's appropriate to continue calling it a "resorbable" implant (although the implant would inarguably be completely "degradable" in the sense of mechanical integrity).

Interactions of different metals and metal ions were also omitted from our assessment. For a pioneering theoretical assessment, it could only be assumed that corrosion would be even, and the release of different metal ions during degradation would also be even; however this is unlikely for a degradable implant in reality. In the body, the release of metal ions, as in any case of corrosion, is expected to be non-linear and multifactorial, affected by engineering parameters such as grain size, manufacturing process, shape, size and surface area of the implant; or non-engineering factors such as pH, ion concentrations, fluid content and pressure at the implant site; plus the often-forgotten yet significant effect of peri-implant fibrous tissues and gas bubbles[58]; although instantaneous fluctuations might be dampened by the buffering ability of bones. Corrosion modelling in various physiological conditions would thus serve as multiple research projects of

considerable sizes by itself, requiring years of joint effort among chemical, medical and engineering researchers. On the biological side, an interaction of various metal ions on the toxicological effects would also be expected, but it also existed as a part of knowledge deficiency in the toxicology of metal ions, and a quantitative modelling of such interaction could only be achieved by extensive studies.

On a related note, while magnesium was erroneously considered by many researchers as "non-toxic"[3, 59, 60], its adverse effects had long been documented[28, 44], and cases of lethality caused by soluble magnesium ions on otherwise healthy individuals were reported[61-64]. The tolerable daily intake of magnesium as food was set at 350-400mg/day[28, 44] for guidance purpose, and the bioavailability of magnesium is about 50%[28], translating into a tolerable mass of implant at 64-73g/year, assuming no intake of magnesium from other routes. Non-fatal, non-gastrointestinal adverse effect due to magnesium (as nausea and hypermagnesaemia) could occur, and diarrhea caused by magnesium overdose is at least partially non-osmotic according to current evidence on its linkage with nitric oxide synthase[65]. Although diarrhea alone is seldom fatal, it can definitely affect the living standard of a patient, and the resultant dehydration and ion imbalance might lead to increased fatality when associated with other diseases and

conditions.

This pioneering risk assessment model should not be considered as a perfect one, and it had been subjected to refinements[66, 67]. Toxicological data might also be overridden by newer, more sophisticated experiments. As the research on degradable metallic implants becomes more popular and metal ions from industrial waste continue to pose health threat to mankind, it is expected that more toxicological studies will be conducted, and international joint programs such as the International Program of Chemical Safety run by WHO, ILO and UNEP[68], or hopefully an establishment of a toxicological database on metals similar to the scale of IPCS, will provide peer-reviewed and updated toxicological guidance limits of metals in the future, so that toxicological risk assessments could be conducted without excessive reliance on data from governments.

The dose of a given substance is an important factor to toxicological effects[69]. Even pure water can kill at a sufficiently high dose[70, 71]. Despite engineering advancements, researchers must realize that degradable metallic implant is not a class of totally inert material, and degradation products do get into the body. As metal ions are released when degradation occurs, it does carry potential side effects that truly require adequate

interdisplinary attention, and cooperation, among engineers, medical doctors, biochemists, medical researchers on toxicology, orthopedics, cardiology, neurology and other areas, plus public health agency officers, before an implant made this class of biomaterial can be considered safe for human use at a considerable dose, i.e. volume.

Conclusion

In this article, dose-response assessment was conducted to derive tolerable limits for alloys that could potentially be adopted as degradable metallic implants. It was found that the limiting factor for the tolerable implant masses of common magnesium alloys was usually aluminum, and the tolerable mass of such alloys at below or around 1 gram per year might be inadequate for applications such as larger internal fixation devices of bone fracture. However, for some component elements such as zirconium and rare earth metals, reliable theoretical assessment could not yet be performed due to a deficit of toxicological data, and toxicological studies should be conducted in the future for such elements to ensure the safety on their use in degradable biomedical implants.

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Statement on the impact

Current researchers on degradable metallic implants sometimes study *in vivo* models or with cell line, but it appears that the majority of articles are on degradable magnesium implants mainly focus on corrosion control and mechanical properties. Even for the *in vivo* models, it appeared that their focus was the localized effects. Insufficient attention was paid to potential systemic adverse effects, and some researchers even assumed magnesium alloys to be completely non-toxic. This is very dangerous, as nothing is totally non-toxic.

This short article utilized the methodology of dose-response assessment, adopted by World Health Organization and most public health agencies, to state the important issue of potential metal toxicity in degradable metallic implant. The possibility of remnant particles after degradation is also briefly discussed.

By attracting the attention of toxicologists, it is hoped that future researchers will be more aware of the toxicological issues of alloying elements, to ensure that future implants will at least be theoretically tolerable to the body.