Gottfried Schmalz
Dorthe Arenholt-Bindslev

Biocompatibility of Dental Materials
Biocompatibility of Dental Materials

With 302 Figures and 82 Tables
The question of whether and to what extent dental materials may be hazardous to patients, the environment, and dental personnel has become of increasing public concern. The very emotional discussion in the public media about amalgam has significantly contributed to this dispute. In addition, reports about potential health risks in relation to other dental materials, such as resins and dental alloys, have generated an increased public and professional interest in this topic. One consequence of this tendency is that dental materials are now the subject of special regulations and directives in almost all countries of the world, intended to guarantee efficiency, safety, and quality and to make sure that only biocompatible materials are brought on the market. Basically, manufacturers are responsible for the safety and quality of their medical devices. It is, however, the responsibility of the dentist to fulfill distinct assignments in this context: The dentist is thus responsible for choosing the most suitable material for each specific indication in an individual patient. Furthermore, the dentist is the primary contact person for patients who have questions about the biocompatibility of the applied materials and is therefore an important part of the market surveillance system, with the responsibility to report adverse effects to the relevant authorities.

For the practicing dentist, it is therefore highly germane to be familiar with the field of biocompatibility of dental materials, which tightly interconnects modern dentistry with other medical disciplines, biology, chemistry, and physics. The first part of the book (Chaps. 1–3) reviews relevant background information on biocompatibility (definitions, determination of biocompatibility, and regulations and standards) in order to qualify the dentist to critically review data and information provided by the manufacturers and marketing companies. The biocompatibility aspects are reviewed in the second part of the book (Chaps. 4–11), structured by groups of materials. The third part of the book (Chaps. 12–14) is devoted to special topics that are of particular clinical and current relevance (environment, occupational hazards, diagnosis of side effects). To ensure the readability of each individual chapter, some aspects are approached from different scopes, and some topics are thus mentioned in more than one chapter, although with different approaches.

The editors are grateful to the publisher for providing the possibility of including a great number of colourful illustrations and clinical pictures. To further enhance the readability of the book Key Notes and Clinical Practice Advices have been highlighted all through the texts, and at the end of each chapter a comprehensive summary of key points have been underlined in Conclusions for the Dental Practitioner.

The guiding theme of all parts of the book was to provide a scientifically based background that should be helpful for the practicing dentist in his or her daily routine and not least form an objective basis for information and discussions with patients presenting individual needs and concerns. The editors of this book recognize that the field of dental biomaterial science is subject to permanent and partly very rapid development and supplementation. Considering this, the authors have intended to present data and concepts of biocompatibility that are currently available. We would like to thank all authors for their diligent work in preparing their texts and for their patience in adjusting the manuscripts.

For the editors and a number of authors of this book, English is not their mother language. The editors are therefore very grateful to Prof. Dr. Werner Geurtsen for his substantial input in providing an English text version of most chapters. The authors thank the publisher, especially Ms. Schröder, Ms. Himberger and Ms. Kaschubowski, for the efficient language editing process and for the important and helpful assistance during the publishing process. Furthermore, the editors would like to thank all those persons who contributed with their professional advice (Dr. H. Claus, Prof. Dr. S. Halbach, Dr. H.-P. Keller, attorney R. Krouskey, Prof. Dr. M. Landthaler, Prof. L. Magos, Dr. A. Petermann, Prof. Dr. H.v.
Philipsborn, Dr. C. Schorn, Prof. Dr. H. Schweikl) or corrected the text (Ms. B. Bey, Dr. T. Bimmerle). Our thanks are also due to our secretaries, in particular Ms. B. Nothaas, K. Eichinger, and K. Roeder. We would like to also thank those colleagues who provided illustrations, which make many aspects of the text more descriptive. Last but not least, we would like to thank the publisher and their editors, whose persistent requests and helpful editorial hints made this book possible.

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### 4 Dental Amalgam

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1.1 Introduction

During the past few years, the biocompatibility of dental materials has evolved into a comprehensive, complex, and independent discipline of dental materials science. Consequently, a number of terms have been developed or were adopted from toxicology. Some of these terms may be familiar to patients and dentists from daily life – for example, the term “safety.” Their exact definitions within the framework of biocompatibility are, however, not always well understood. To avoid misunderstandings and to allow discussions between dentists, manufacturers, and patients at an objective and scientific level, certain knowledge of some fundamental terms and aspects of biocompatibility is necessary. This chapter is an introduction to the field.

Like many other disciplines, the field of biocompatibility has been trying to agree on generally accepted definitions of terms. However, this has not always been successful. Thus, the following definitions are based on general concepts of biocompatibility as they are frequently used in the literature and in standards [1, 8–11].

**Biomaterial** refers to any nonvital material intended to interact with biological systems within or on the human body. Dental materials inserted into the oral cavity therefore belong to the group of biomaterials. As such, they are subject to specific legal regulations, a situation that in turn has a direct influence on daily dental practice (see Chap. 3). Worldwide, most countries allow the use of only those dental materials that have successfully passed a special certification process (Fig. 1.1).

**Biocompatibility** (or tissue compatibility) describes the ability of a material to perform with an appropriate host response when applied as intended. A biocompatible material may not be completely “inert”; in fact, the appropriateness of the host response is decisive. This adequacy is generally assessed by various experts according to specific guidelines in which a comparison with products that are already on the market plays an important role. Because there is always a possible range associated with these assessments, evaluations may not generate identical results. It is thus the dentist’s obligation not to rely on these assessments blindly but rather to question them critically.

Besides this classic concept of biocompatibility (inert/tolerable biomaterial), the targeted influence of a biomaterial on the metabolism of adjacent cells has gained an increasingly important function (bioactive materials). Surfaces of materials can be specifically pretreated (“biofunctionalized”), such as by coating a titanium surface with signaling proteins (e.g., bone morphogenetic protein to improve the attachment of bone tissue). Regarding bone regeneration, the
term “osteconductive material” is used for materials serving as scaffolds for the ingrowth of preosteoblasts, whereas osteoinductive materials induce formation of new bone by the differentiation of pluripotent local connective tissue cells into bone-forming cells.

The biocompatibility of a material is mainly determined by its release of substances through solubility or corrosion. These substances may damage cells, or, by stimulating cellular synthesis of certain proteins (e.g., pro-inflammatory mediators such as interleukin-1 and interleukin-6), induce inflammation. Likewise, the surface absorption or accumulation of proteins, or the interaction of a material with the extracellular matrix, is important for the biological behavior of a material (for example, the attachment of cells/bacteria on material surfaces). The adhesion of proteins (e.g., the formation of a pellicle by saliva proteins) is influenced by a material’s chemical properties as well as its physical characteristics (e.g., wettability, surface energy).

**Tissue engineering** is a comparatively new area of biomaterial application. It is the science of design and manufacture of new tissues for the functional restoration of tissues and organs (regenerative medicine/dentistry). Nondegradable and (mainly) degradable biomaterials serve as scaffolds for signaling molecules or cells, or both, and they are designed to actively interfere with adjacent body cells.

**Safety** in relation to the evaluation of (dental) biomaterials means freedom from unacceptable risks. Thus, safety does not stand for a complete lack of risks. As with the definition of the term “biocompatibility”, adequacy has an important function with respect to safety.

**Side effects** of a biomaterial are defined as those effects that, besides the intended main function, are also characteristic for this biomaterial but are not wanted. A synonymously used term is “adverse effects.”

**Toxicity** of a material describes the ability to damage a biological system by chemical means. In higher organisms (animals, human beings), local toxicity – that is, adverse reactions emerging at the application site – is differentiated from systemic toxicity, in which adverse reaction appear in an area distant from the application site. In dentistry, local reactions primarily occur in the pulp, the periapical periodontium, and the gingiva/oral mucosa.

**Immunotoxicity** of a material describes adverse effects on the structure and function of the immune system, for instance on relevant cells such as monocytes. These effects impair the host defense (e.g., against infection) or may cause tissue damage, such as by chronic inflammation.

### 1.2 Health Effects

**Key Note**

Dental materials may cause adverse health effects. In dental patients, the frequency of these effects lies within the range of one-tenth of a percent and is thus very low [12, 20]. For comparison, an epidemiologic survey in the United Kingdom in 2004 revealed that 23% of women and 13.8% of men experience some sort of adverse reaction to a personal care product (such as cosmetics) over the course of a year [18]. The incidence of occupational health complaints in dental personnel is considerably higher. Among dental personnel, 40–50% report work-related health problems, primarily related to latex gloves, followed by acrylates (see Chap. 12).

Health effects can be subdivided into the following:

- Systemic toxicity
- Local reactions
- Allergic reactions
- Other reactions

**Fig. 1.1** Only those biomaterials (medical devices) that are labeled “CE” may be used in dental practice in the European Union
1.2.1 Systemic Toxicity

Almost all dental materials release substances into the oral cavity, from where they may enter the human body through different routes, including swallowing of saliva and inhalation, with subsequent passage of the epithelial barriers in the gastrointestinal tract or the lungs. These substances may, via the blood circulation, be transported to different organs. The application site may thus be in a different location from the effect. At the location of the effect, there may be interference with the function of the specific organ if the concentration is sufficiently high (systemic toxicity). According to the time frame, acute (up to an exposure period of 24 h), subacute (up to 3 months), and chronic toxicity are differentiated. A considerable number of single case reports published in the literature, in particular in the lay press, have claimed to present mainly chronic side effects of dental materials. Examples of such materials are amalgams, resin-based composites, and dental alloys. However, scientifically based literature reviews clearly show that a causal relation between chronic general health complaints and exposure to dental materials has very rarely been found (see Chaps. 4–9). Patients may thus feel a need for thorough information about safety aspects, so dentists need to be familiar with this topic to be able to supply their patients with correct and adequate information.

1.2.2 Local Reactions

Substances released from dental materials may generate a reaction (e.g., inflammation or necrosis) in adjacent tissues (local toxicity), such as oral mucosa/gingiva (Fig. 1.2), pulp (Fig. 1.3), or alveolar bone. Cytotoxicity refers to damage to individual cells, for example in cell cultures. Cells can die because of necrosis or apoptosis (programmed cell death). Furthermore, if cell metabolism is influenced, the release of pro-inflammatory mediators may be the consequence.

However, factors other than substances released from dental materials may cause a local tissue reaction. Of these, the presence of bacteria that accumulate at the surface, at the margin, or under a material is the most important factor (Fig. 1.4). Numerous studies and reports in the scientific literature address these mechanisms. Mechanical/physical irritation, such as pressure caused by dentures, can also cause local tissue reactions. Local reactions are quite often seen in dental practice, and a correct diagnosis is thus of great importance.

1.2.3 Allergies

An allergic reaction to a substance can be triggered if the organism was previously sensitized to this compound. Four different types of allergic reactions are differentiated (Table 1.1). Types I, II, and III are mediated by antibodies (IgE, IgG), whereas type IV is primarily imparted by cells. Dental materials may cause allergies of type I (immediate reaction) and type IV (delayed reaction). The concentrations that elicit a reaction in a previously sensitized person vary between subjects. The dose levels causing allergic reactions are generally significantly lower than those causing toxic reactions. Substances may be released from dental...
materials into the oral cavity at dose levels sufficiently high to elicit allergic reactions in previously sensitized individuals. Allergic reactions elicited by dental materials can occur intraorally or as remote reactions extraorally, such as reactions associated with nickel exposure (Figs. 1.5–1.7).

Allergies to various substances can occur simultaneously. A cross-sensitivity is assumed if allergies to chemically-related substances occur in a patient. Examples are nickel and palladium, which belong to the same main group in the periodic table of elements. Patients who suffer from an allergy to nickel are very often also allergic to palladium [5]. This must be kept in mind if palladium-containing alloys are used for restorative purposes. Cross-reactivity to chemically-related methacrylates is also known (see Chap. 14).

A concurrent sensitization is generated by two allergens that are frequently present at the same time in the environment or in a material and thus by parallel exposure may sensitize an individual and/or elicit positive reactions in allergy testing.

Numerous reports and studies about the allergenic properties of dental materials have been published in the scientific literature (see also Chap. 14). Allergies that are associated with dental materials are of increasing importance, not least due to the marketing of new resin monomers. Reactions in patients and particularly in dental personnel may have an allergenic origin.

A position paper on chemicals and contact allergens was recently published by a German health authority [13]. Accordingly, contact allergy is classified into three categories:

- A: Important contact allergens
- B: Suspected contact allergens in humans
- C: Unimportant contact allergens

A number of substances that are components of dental materials belong to category A, including Perubalm, bisphenol A diglycidyl ether (BADGE), certain methacrylates, formaldehyde, and glutaraldehyde (see Chap. 14).

1.2.4 Other Effects

This group includes mutagenic, carcinogenic, and teratogenic effects. Substances released from materials can cause alterations of the genome DNA (genotoxicity). Cells possess a number of mechanisms to repair genotoxic damages. Alternatively, a transfer of these genetic damages to subsequent generations of cells can be avoided by programmed cell death (apoptosis). Nonetheless, if these genetic damages are passed on to the next generation, this effect is called mutagenicity. Some materials or substances released from them may also basically promote the generation of malignant

<table>
<thead>
<tr>
<th>Table 1.1 Types of allergic reactions</th>
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<tbody>
<tr>
<td>Immediate reaction, anaphylactic (Type I)</td>
</tr>
<tr>
<td>Cytotoxic reaction (Type II)</td>
</tr>
<tr>
<td>Formation of immune complexes (Type III)</td>
</tr>
<tr>
<td>Delayed reaction (Type IV)</td>
</tr>
</tbody>
</table>
tumors; in other words, they have a carcinogenic effect. Mutagenicity can be assessed as an indicator of possible carcinogenicity of substances that directly attack DNA.

It is known that certain substances (thalidomide, for example) may cause malformations during embryonic development (teratogenicity). Thus, substances leaching from materials should be evaluated for their potential risk of causing a teratogenic effect (see Sect. 1.3.2). This also applies regarding a possible influence on reproductive ability.

In relation to dental materials, the aforementioned health effects belonging to this group are generally more theoretical, since up to now no such damages have been clinically observed subsequent to the application of dental materials.

### 1.3 Risk

According to EU regulations the intended use and the duration of the intended exposure period determine the extent of biological assessment prior to marketing, for which the manufacturer is responsible. This information is the basis for the manufacturer’s information to the dentist, who is responsible for passing the relevant information on to the staff as well as to the patients. The degree or extent of possible health damage is described by the term “risk.”
Key Note

In the context of biocompatibility, risk means the combination of the probability of occurrence of harm (side effect) and the severity of that harm. An important basis for evaluating a risk is the detailed knowledge about the composition of a material, including possible contaminants.

The following factors need to be considered in the risk assessment of a material: the exposure route, the duration of the intended contact with vital tissues, the hazards potentially associated with the application, and the character of the leaching substances.

1.3.1 Risk Analysis

Risk can be evaluated according to methods that are recommended by standard guidelines (e.g., ISO 14971) [3, 10]. The first step is risk analysis, which comprises the systematic use of available information to identify hazards and to estimate the risk. Risk analysis is subdivided into different segments (Fig. 1.8) and includes identification and evaluation of possible damages considering the effective exposure. The aim of risk analysis is to assess or predict the probability and the degree of effects of a material on human health and to create guidelines for its use, if necessary.

1.3.2 Risk Evaluation/Risk Perception

Risk evaluation must be distinguished from risk analysis (see Fig. 1.8). Risk evaluation addresses the question of whether a risk can be accepted or not by comparing the estimated risks against given risk criteria. An important factor, besides the results of the risk analysis, is the expected benefit. Risk evaluation also incorporates socioeconomic factors of the specific society. Both, risk analysis and risk evaluation are summarized as risk assessment. This risk assessment – based on statistical data (probability calculation) – must be differentiated from the perception of a risk in the general population. Tables 1.2 and 1.3 summarize the risks of daily life and the risks when using various drugs. It is obvious that the general population currently accepts various risks even though they are associated with comparably high death rates, such as riding a motorbike. Some risks are even connected with a positive image, for instance in terms of challenging one's strength (“No risk – no fun”).

The public perception of risk is intuitive. In particular, in cases of uncertainty, objectively low risks are frequently overestimated. Thus, a balanced “risk communication” between dentist and patient is of high importance. An important goal is that the discrepancy between objective risk assessment and intuitive risk perception is clearly demonstrated by precise examples.

Fig. 1.8 Schematic representation of the risk management process [10]
1.3.3 Risk Management

Risk management includes all steps of risk analysis, risk evaluation, and risk control (see Fig. 1.8). Warning notices about particular risks in the user’s information (for instance, “allergenic”) may reduce the risk, since the frequency of unwanted side effects may be minimized by precautionary measures such as nonapplication in cases of supposed allergy. Such warning notices can be found as symbols printed on the wrapping of dental materials (see also Chap. 3).

1.3.4 Threshold Values

Threshold values are defined by national and international boards and are intended to serve as points of reference. Frequently, specific threshold values are used for assessing biocompatibility (NOEL, NOEAL, LOEL, LOAEL). Furthermore, threshold values are also defined for administrative purposes (TI, TDI, TWI, STEL). In dentistry, these values mainly apply to systemic toxic reactions. Definitions of important threshold values are summarized in the appendix of this chapter.

1.4 Effective Dose/Concentration

1.4.1 Principle of Dose

Paracelsus pointed out as early as the 16th century that toxic reactions are dependent on the dose (“Dosis facit venenum”). This principle still applies. The concentrations necessary to trigger an allergic reaction are individually different and are much lower than those that elicit toxic reactions.

For dental materials, “dose” means the amount of substance that is released from a specific material. The dependence of the toxic reaction on the dose is exemplarily illustrated in Fig. 1.9, regarding nickel ions that were added to cell cultures. There is obviously a dose–
reaction curve, meaning an elevated toxicity with increasing concentration: 0% on the y-axis means that all cells are dead, and 100% means that all cells are viable. Below a certain dose, no reaction occurs; this is the “threshold dose.” This principle, which is known from toxicology, means that there might be no toxic reaction if the amount of substances released from a material is very low. However, alterations of the genome (DNA) are exceptions to this principle because up to now no threshold dose can be documented for these damages.

1.4.2 Effective Versus Applied Dose

One needs to differentiate between effective dose and applied dose. The effective dose is available at the target organ, but is different from that at the application site, because absorption, transportation, and metabolism will take place between both locations. For instance, only 7% of the Hg\(^{+2}\) ions that are released from amalgam into saliva will, in fact, be absorbed in the gastrointestinal tract, subsequently distributed via the blood circulation, and then transported to the target organs (such as the kidneys). Thus, the orally applied dose (that is, the concentration in saliva) is significantly different from the effective levels at the target organs. Absorption, transportation, and metabolism of various substances are very different. Another example is that the effective concentration of a substance released from a restorative material (eugenol, for instance) is significantly lower in the pulp than at the cavity floor. Therefore, zinc oxide and eugenol cements clearly have an antimicrobial action (are toxic to bacteria) at the cavity floor, but pulp cells will not be damaged if the dentin is not perforated.

Key Note

For the clinician, it is very important to differentiate between applied and effective dose. For instance, readings of salivary metal concentrations are of little significance because these values represent only the applied dose, which can be considerably different from the effective dose.

1.4.3 Low-Level Dose Range

Long-term and low-level dose exposure is of special interest in the current public discussion about chronic toxicity. This subject is well known from public debate about environmental issues, and similar concern has been raised about dental restorative materials such as composite resins and amalgam. Currently, new analytic methods are being developed that allow the detection of minute amounts of a chemical substance, specifically of metals, with highly sensitive analyses.

Key Note

The presence of a substance in tissue is not equivalent to a toxic effect, but the dose is decisive.
accumulation of bacteria, for instance at the surface of composite resins (Fig. 1.10). Hence, the risk associated with a substance has to be carefully assessed for each clinically relevant exposure before a recommendation can be given.

1.4.4 Placebo/Nocebo Effect

The placebo effect means that an effect will be observed without the application of an active ingredient. This phenomenon is well known in pharmacology. This placebo effect may be due to an extrinsic effect or to an autosuggestion [16]. Equivalently, adverse effects may occur even if no active ingredient is applied; this is known as the nocebo effect. Translated into biocompatibility, this means that belief in the harmfulness of

![Fig. 1.10 Accumulation of bacteria on the surface of a luting composite](image)

<table>
<thead>
<tr>
<th>Nocebo effect</th>
<th>Percentage of incidence of unwanted effects</th>
<th>Placebo (P)</th>
<th>Active drug (A)</th>
<th>Difference (A – P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>32</td>
<td>56</td>
<td>+24</td>
<td></td>
</tr>
<tr>
<td>Drowsiness</td>
<td>21</td>
<td>29</td>
<td>+8</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>30</td>
<td>32</td>
<td>+2</td>
<td></td>
</tr>
<tr>
<td>Faintness</td>
<td>6</td>
<td>13</td>
<td>+7</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>24</td>
<td>50</td>
<td>+26</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>20</td>
<td>30</td>
<td>+10</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>9</td>
<td>8</td>
<td>–1</td>
<td></td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>15</td>
<td>23</td>
<td>+8</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>19</td>
<td>15</td>
<td>–4</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>8</td>
<td>17</td>
<td>+9</td>
<td></td>
</tr>
<tr>
<td>Anxiety state</td>
<td>25</td>
<td>33</td>
<td>+8</td>
<td></td>
</tr>
<tr>
<td>Impaired vision</td>
<td>18</td>
<td>20</td>
<td>+2</td>
<td></td>
</tr>
<tr>
<td>Eczema</td>
<td>4</td>
<td>16</td>
<td>+12</td>
<td></td>
</tr>
<tr>
<td>Itching</td>
<td>10</td>
<td>16</td>
<td>+6</td>
<td></td>
</tr>
</tbody>
</table>
a material may cause the symptoms of disorders. Frequently, symptoms associated with the testing of drugs are characterized by a disturbed existential orientation (psychosomatic disturbances; see Table 1.4).

Interestingly, patients who claim dental materials to be the reason for their disorders reveal similar symptoms as those mentioned above. Nocebo effects can be triggered or enhanced in anxious patients because of the suggestive genesis, by fearful imaginations, and also by reports in the media [16]. The dentist should, therefore, thwart these fears by providing correct information.

1.5 Interdisciplinary Collaboration

A close collaboration of different medical disciplines is required to evaluate biocompatibility and to handle patients who allege assumed or real adverse effects to dental materials. The dentist has an important function in this team, including providing information about the composition of a material or of specific circumstances in a patient’s oral cavity (such as bruxism) and establishing differential diagnoses. The treatment of patients who claim a material-related health problem should always begin with a comprehensive dental examination and treatment. A dermatologist must be consulted in a case of suspected allergy, but the dentist is responsible for providing the necessary information (case history, symptoms, composition of the suspected material, and so on). Furthermore, to avoid unnecessary allergy tests, the dentist has to be familiar with the problems associated with them. Patients who claim material-associated damage frequently specify various disorders for which the reported symptoms are very general and may also be caused by internal diseases or drug therapy. A close collaboration with the family doctor, a specialist in internal medicine, or another medical specialist is necessary in these cases.

A possible psychiatric disorder must be also considered, even though most patients will perceive this possibility very negatively. A number of scientific studies have clearly shown that patients with claimed material-related disease may also suffer from a mental disturbance [6].

Last but not least, it has to be accepted that in some cases, no cause may be found for symptoms or disturbances of existential orientation. Unfortunately, this fact is often not accepted in traditional dentistry, with its mainly mechanistic focus compared to general medicine (and also due to expectations of the patients). But some patients are indeed relieved to hear that their symptoms are not the sign of a malignant disease or tumor.

Close collaboration among various disciplines is possible in specialized medical centers. Treatment of patients with a claimed material-related disorder is extremely time-consuming; a comprehensive dental and medical examination will often take several hours.

Conclusions for the Dental Practitioner

1. Dental materials are biomaterials and, therefore, are subject to specific legal regulations and standards.
2. Dental materials may cause various side effects. The frequency in patients, however, is very low (in the range of tenths of a percent) but is significantly higher in dental personnel. Local reactions and allergies represent the most important side effects.
3. Patients’ risk perception is often very different from the scientifically based risk (risk analysis/risk evaluation). In this context, the dentist should provide objective information. A correlation to other risks of daily life may be very helpful for many patients to enable them to rank risks more objectively and realistically.
4. Treatment of patients with claimed or real side effects caused by dental materials will often be successful only if specialists of various medical disciplines collaborate very closely. Severe cases are rare, but the treatment of each individual patient requires much time and experience.

Appendix

LOEL: Lowest Observed Effect Level. Lowest concentration or amount of a substance, found by experiment or observation, that causes any alteration in morphology, functional capacity, growth, development, or life span of target organisms distinguishable from normal (control) organisms of the same species and strain under the same defined conditions of exposure [17].
LOAEL: Lowest Observed Adverse Effect Level. Lowest concentration or amount of a substance, found by experiment or observation, that causes an adverse alteration of morphology, functional capacity, growth, development, or life span of target organisms distinguishable from normal (control) organisms of the same species and strain under defined conditions of exposure [17].

NOEL: No Observed Effect Level. Greatest concentration or amount of a substance, found by experiment or observation, that causes no alterations of morphology, functional capacity, growth, development, or life span of the target organism distinguishable from those observed in normal (control) organisms of the same species and strain under the same defined conditions of exposure [17].

NOAEL: No Observed Adverse Effect Level. Greatest concentration or amount of a substance, found by experiment or observation, that causes no detectable adverse alteration of morphology, functional capacity, growth, development, or life span of the target organism under defined conditions of exposure [17].

The following threshold values have been defined for administrative purposes based on risk assessments:

STEL: Short-Term Exposure Level. Concentration to which workers can be exposed continuously for a short period of time without suffering from irritation, chronic or irreversible tissue damage, narcosis of sufficient degree to increase the likelihood of accidental injury, impaired self-rescue, or materially reduced work efficiency.

TI: Tolerable Intake. Maximum amount of a xeno-biotic (in correlation to body weight) that can be ingested over time by the human organism without causing damage, usually indicated in mg/kg/time unit.


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2.1 Introduction

Dental materials may result in damage to various tissues. Therefore, a great variety of different test methods are applied to evaluate the risk of such damage to ensure material compatibility prior to market launch. However, the results of such evaluations are dependent not only on the tested material but also on the test method used. The findings of these studies and the resulting claims of the manufacturers should be critically challenged by the dentist, so dentists need to be familiar with the principles and, in particular, with the problems of these test methods. This chapter describes and assesses the fundamental and frequently used methods for evaluating the biocompatibility of dental materials (see Sect. 2.2).

Even if the risk of damage caused by a new material is considered to be acceptable, it has to be kept in mind, not least due to the frequently high number of subjects who will come into contact with this material, that some patients may reveal problems based on specific circumstances – in other words, the problem of individual compatibility. This problem is addressed by certain test methods applied on individual patients, such as allergy tests. These diagnostic tests will be discussed in the second part of this chapter (Sect. 2.3).

2.2 Evaluation of Materials

2.2.1 Principles of Biocompatibility Testing

2.2.1.1 Overview of Test Methods

Evaluation of the biocompatibility of dental materials is a complex and comprehensive area because unwanted tissue reactions may occur in a great variety of types. An overview of common test methods is given in Table 2.1. Any single test method is applicable only for investigating one type of unwanted reaction out of a great variety of possible reactions. For instance, the so-called pulp/dentin test can be applied to determine the pulpal compatibility of a new material (local reaction), but it cannot be used to determine its allergenic potency.

Moreover, individual test methods are usually adequate only to describe or document a single aspect of a certain type of unwanted reactions. For example, cell culture tests will detect only the influence of a material on isolated cells. These findings cannot be transferred to patients without limitation. An alloy that does not cause a reaction in cell cultures may very well result in problems in patients because there may be a lower pH value below plaque or in crevices (e.g., telescope crowns) in the oral cavity. This lower pH value may result in a more pronounced corrosion of the alloy in vivo compared to the neutral conditions in cell cultures. However, cell culture findings may help explain the mechanisms of an unwanted reaction in a patient, for instance, an inflammation of the gingiva.
### Key Note

Biocompatibility of a material cannot be evaluated by using a single test rather than a group of various techniques.

#### 2.2.1.2 Phenomena and Mechanisms

Dentists and patients are primarily those who ask whether a material may be harmful for the patient or dental personnel, how this possible damage would become manifest, how it could be prevented, and what countermeasures are available. These questions can be answered by clinical investigations and observations as well as by animal studies, mainly on larger animals such as primates or dogs. These animal models are adequate for the best possible simulation of a material's application on patients (usage tests). The focus of these animal studies is the observed phenomenon and its transfer to the patient. However, for the further development (improvement) of dental materials and their overall assessment, the answer to the question of why a certain unwanted reaction occurs is decisive. Therefore, it is necessary to clarify the mechanism of an observed phenomenon – that is, the unwanted reaction. For this purpose, studies with smaller experimental animals (e.g., rats or guinea pigs) or cell cultures are performed.

#### 2.2.1.3 Strategies for Evaluating Biocompatibility

The common approach and principle when testing the biological behavior of materials is to start with simple in vitro tests mostly based on cell cultures, as is generally done in toxicology. If these experiments and investigations of a material's efficiency deliver promising findings, then more comprehensive studies on experimental animals and usage tests (in vivo evaluation) will be performed. Clinical studies are the final step of this evaluation process.

However, some materials (e.g., zinc oxide and eugenol cements) have caused toxic reactions in cell cultures whereas no damage was induced in patients (in this case, no pulp reactions); indeed, valuable therapeutic properties such as pain relief were revealed. Thus, the aforementioned more schematic approach is increasingly being abandoned. Today's focus is an initial risk assessment by an expert. In this process, data already available about physical, chemical, and biological characteristics are evaluated, and a decision is made regarding whether further studies are necessary at all. If a material that has already been applied in practice was only slightly modified, then its harmlessness (i.e., acceptable risk) can be certified, for example, based on the chemical analysis of extracts (see below). If, however, further biological tests are necessary – for instance, because the formulation has considerably

### Table 2.1 Selection of usual test methods for assessing the compatibility of dental materials

<table>
<thead>
<tr>
<th></th>
<th>Systemic reactions</th>
<th>Local reactions</th>
<th>Allergic reactions</th>
<th>Other reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In vitro</strong></td>
<td>(Cell cultures can be used for specific problems)</td>
<td>Cell cultures – Agar overlay – MTT test – Dentin-barrier test</td>
<td>(Cell culture models are currently being developed)</td>
<td>Mutagenicity – Ames test – Micronucleus test – HPRT test – Mouse lymphoma test</td>
</tr>
<tr>
<td><strong>Animal experiments</strong></td>
<td>Acute LD$<em>{50}$ (e.g., oral application) Chronic LD$</em>{10}$ (e.g., oral application)</td>
<td>Implantation tests – Pulp/dentin test – Endodontic test – Implantation test</td>
<td>Maximization test with modifications Local lymph node assay</td>
<td>Micronucleus test (rodents) Teratogenicity (rodents) Reproductive toxicity (rodents)</td>
</tr>
<tr>
<td><strong>Patient</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
<td></td>
<td></td>
<td>(Occupational exposure, poisoning)*</td>
</tr>
</tbody>
</table>
changed or new components are used – then in vitro tests will be performed first. Subsequently, the risk will be reassessed, followed by more tests if needed (Fig. 2.1). The formal approach is regulated by standards. This policy, which appears rather complicated at first glance, has the advantage that each material will be individually assessed. This may save unnecessary animal experiments and allow a faster market launch of materials. But it must be emphasized that the assessing experts and the manufacturers have to bear a particular responsibility [86] (see also Chap. 3).

**Key Note**

It is important for the clinician to realize that experiences with premarket evaluation and certification systems, even those based on legal regulations, have revealed that assessment results must be critically questioned. For instance, filling materials that had successfully passed such a test system were introduced on the market without previous clinical studies. In daily practice, however, these materials generated severe side effects including pain and tooth fracture (refer to Sect. 2.2.7: Figs. 2.15 and 2.16) [12].

### 2.2.2 Test Materials

The biocompatibility of a material can be determined directly or by using an “extract.” In the first case, tissue will be directly exposed to the material, whereas in the second case, the material will be stored under specific conditions (e.g., defined by standards) for a certain time (e.g., 24 h) at a specified temperature (e.g., 37°C) in a liquid. Subsequently, this “loaded” liquid, known as extract or eluate, will be used for further tests. A chemical analysis of these extracts may already provide valuable information regarding the “leaching behavior” of materials. Hydrophilic liquids (e.g., saline solution) or lipophilic fluids (e.g., dimethyl sulfoxide, or DMSO) are used for extractions. Mixtures (ethanol/water) are also used as extraction fluids [27, 34].

Interestingly, almost all materials release the major share of their releasable components when they are not set or shortly after mixing. This is exemplified in Fig. 2.2, which demonstrates the release of fluoride from filling materials. An important conclusion from these findings is that dental personnel, who may have intensive contact with unset materials, may be exposed
to very high concentrations of released substances and thus should be considered a risk group (Fig. 2.3).

### 2.2.3 Systemic Toxicity

Experimental animals are usually used to determine systemic toxicity. The test substances can be administered in various ways. In dentistry, most substances or materials are administered orally (feeding of an extract or of the test material, mostly finely ground). Previously, the acute LD$_{50}$ (see Appendix) was determined as routine. Today, other methods that are more sparing of animals are used, such as the so-called limit test (administration of a fixed dose, e.g., 2,000 mg/kg body weight). If this concentration is not high enough to reach the LD$_{50}$, then generally no further tests will be done, and the material will not be placed in the categories of “very toxic” to “minor toxic,” according to Table 2.2 [76].

The chronic systemic toxicity will be determined by administering the material or extract over several months. Tests are sometimes extended over the lifetimes of the experimental animals. At the end of these studies, survival rates of the animals and pathohistological alterations of the main organs will be determined.

Besides these classic systemic toxicity tests, additional methods may have to be used to answer special questions, such as those regarding genetically modified animal strains. Further information regarding chronic toxicity is obtained from accidents (high exposure level) and based on observations of occupationally exposed subjects (e.g., dental personnel) who are often in contact with the “active” unset material. Substances can be classified in various toxicity categories according to relevant guidelines (Table 2.2).

**Assessment:** In the past, data about acute systemic toxicity were routinely presented to assess a material according to relevant legal regulations and standards. Unfortunately, this information is often not published and thus is not accessible for scientific discussion [109]. Available data regarding acute LD$_{50}$ (Tables 2.3 and 2.4) indicate, however, that dental materials are characterized by a low acute systemic toxicity in general [87].

Only rare findings are available regarding systemic toxicity of dental materials due to chronic exposure. Dental amalgam represents an exception: Comprehensive data about many different aspects after chronic exposure have been published, specifically addressing mercury toxicology (see Chap. 4). Today, the significance of the aforementioned preclinical tests to evaluate the systemic toxicity of dental materials is generally considered low. At least, it no longer seems appropriate to determine a classic LD$_{50}$ [109].

### Key Note

Findings from preclinical tests to determine the systemic toxicity of dental materials are usually of little clinical relevance for the dentist. Such tests are applied for assessing new materials before they are introduced on the market in order to fulfill legal requirements. Of special importance, however, is the analysis of risk groups, such as dental personnel.

### 2.2.4 Local Toxicity and Tissue Compatibility

Local toxicity must be differentiated from local tissue compatibility. Local toxicity is based on the chemical interaction of a toxic substance with biologically relevant molecules. Tissue compatibility, however, may also be dependent on causes other than material toxic-