

## Contents

1.1	Introduction	1
1.2	Health Effects	2
1.2.1	Systemic Toxicity	3
1.2.2	Local Reactions	3
1.2.3	Allergies	3
1.2.4	Other Effects	4
1.3	Risk	5
1.3.1	Risk Analysis	6
1.3.2	Risk Evaluation/Risk Perception	6
1.3.3	Risk Management	7
1.3.4	Threshold Values	7
1.4	Effective Dose/Concentration	7
1.4.1	Principle of Dose	7
1.4.2	Effective Versus Applied Dose	8
1.4.3	Low-Level Dose Range	8
1.4.4	Placebo/Nocebo Effect	9
1.5	Interdisciplinary Collaboration	10
	Conclusions for the Dental Practitioner	10
	Appendix	10
	References	11

## 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 to not 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

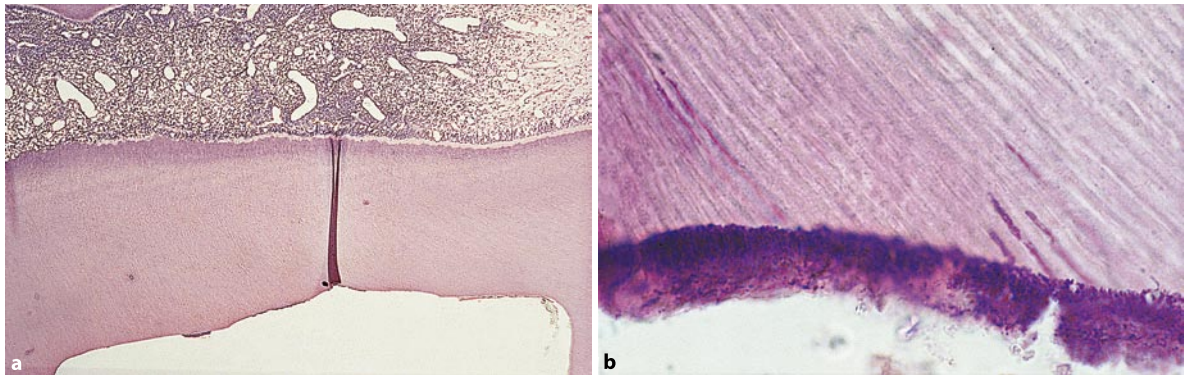
An allergic reaction to a substance can be triggered if the organism was previously sensitized to this compound. Four different types of allergic reactions are differentiated (Table 1.1). Types I, II, and III are mediated by antibodies (IgE, IgG), whereas type IV is primarily imparted by cells. Dental 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



■ Fig. 1.2 Inflammation of the gingiva in contact with a porcelain-fused-to-metal crown



■ Fig. 1.3 Pulp necrosis after application of resin fillings



**Fig. 1.4** **a** Pulp damage caused by bacteria on the cavity floor: pronounced pulp reaction. (magnification  $\times 80$ ) **b** Bacteria on the cavity floor and in dentin tubules, which may be the cause of a pulp reaction (magnification  $\times 400$ )

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 Peru balm, 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 1.1** Types of allergic reactions

Immediate reaction, anaphylactic (Type I)
Cytotoxic reaction (Type II)
Formation of immune complexes (Type III)
Delayed reaction (Type IV)





■ **Fig. 1.5** Allergic contact dermatitis on the fingertip of a dentist after contact with resin-based composite



■ **Fig. 1.7** Allergic reaction of type IV (reaction on the hands, distant from the exposure site) after exposure to nickel during an orthodontic treatment (Courtesy of N. Veien, Aalborg, Denmark)



■ **Fig. 1.6 a** Pronounced gingivitis of an orthodontic patient (nickel-containing device) who revealed a positive reaction in a patch test. The most important differential diagnosis would be “plaque-associated” inflammation. **b** Persisting perioral and labial eczema of an orthodontic patient (copper–nickel–titanium wires). The patient had no intraoral symptoms, and there was complete regression after replacement with titanium wires

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.

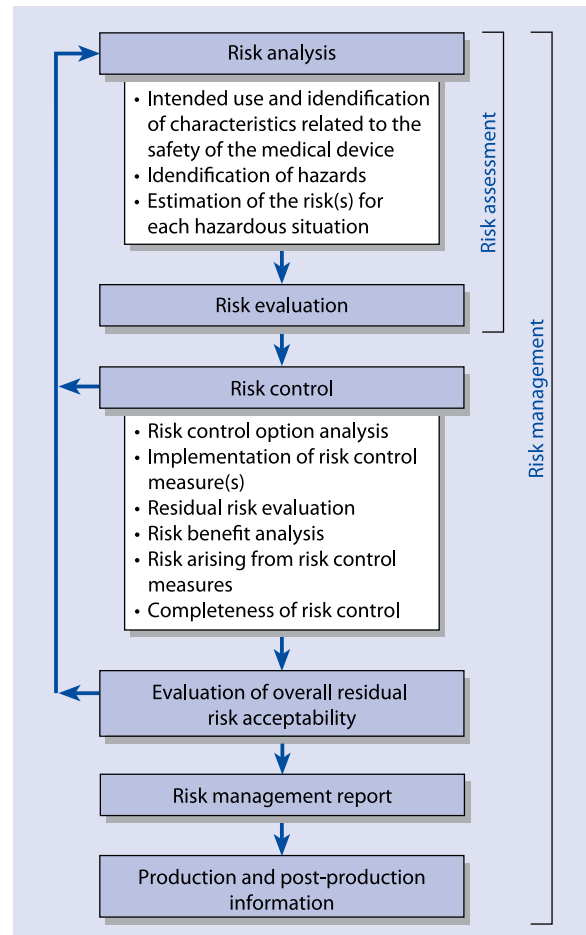
The following factors need to be considered in the risk assessment of a material: the exposure route, the duration of the intended contact with vital tissues, the hazards potentially associated with the application, and the character of the leaching substances.

### 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



■ Fig. 1.8 Schematic representation of the risk management process [10]

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.

## Key Note

It is important for the clinician to be aware that in most cases, a conspicuous discrepancy exists between the patient's risk perception and the scientifically assessed risk. The current public discussion about dental materials is an excellent example of this discrepancy. Thus, an important step toward objectifying the patient's consultation may be to refer to this gap and to the risks of daily life; this can make it easier for the patient to realize and estimate the risk posed by dental materials.

### 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).

Table 1.2 Risks of daily life [14]

Risk	Incidence: one fatality per $x$ number of persons
Bee sting	5 million
Strike of lightning	2 million
Food poisoning	0.8 million
Air travel	0.8 million
Cycling	54,000
Pedestrian	26,000
Active soccer player	6,000
Driving a car	5,700
Motor biking	1,000
Smoking	200

### 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, NOEL, 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

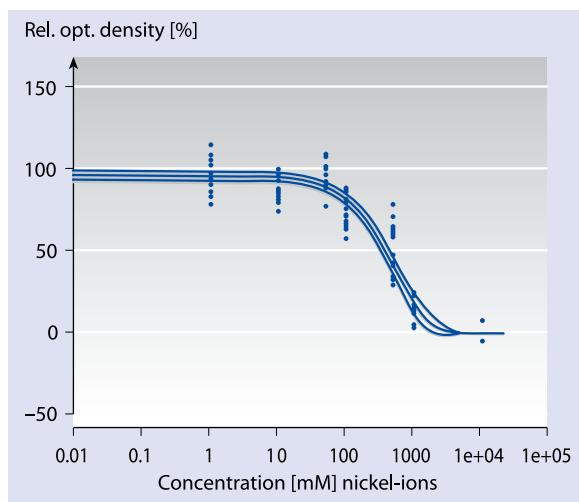
## Key Note

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–

Table 1.3 Real risks of drug-associated side effects [2]

Drug	Fatalities	Treated patients
Digoxin	5	6,612
Heparin	2	2,102
Potassium chloride	1	8,764
Streptokinase	1	7
Allopurinol	1	1,331
Cosyntropin	1	68
Meperidine	1	2,852



■ **Fig. 1.9** Typical dose–response curve: influence of nickel ions on a cell culture. Single measurements are shown in combination with a mathematical calculation of the dose–response curve and a 95% confidence interval

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  $\text{Hg}^{++}$  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 vari-

ous 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

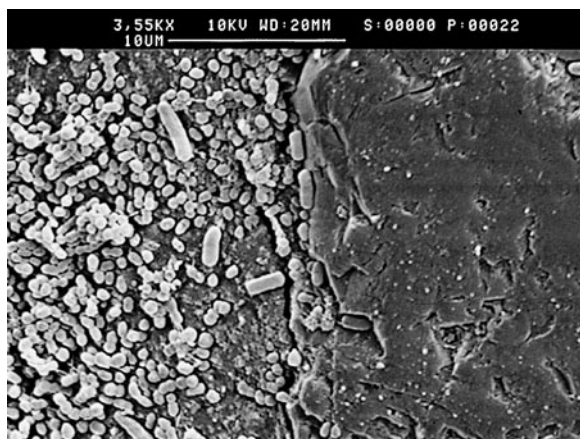
Long-term and low-level dose exposure is of special interest in the current public discussion about chronic toxicity. This subject is well known from public debate about environmental issues, and similar concern has been raised about dental restorative materials such as composite resins and amalgam. 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.

It is not possible to extrapolate from biological reactions caused by high doses and short exposure times to effects associated with low concentrations and long-term exposure. The principle of threshold dose also applies for chronic exposure: Substances do not cause a reaction below a certain dose [16]. This principle is valid for all effects, except for some carcinogens that react directly with DNA. Further, it has to be considered that small quantities of a chemical substance may be beneficial rather than detrimental. For instance, low amounts of methacrylates can significantly promote proliferation of certain bacteria [4, 7, 19]. The clinical consequence of this growth promotion is an





**Fig. 1.10** Accumulation of bacteria on the surface of a luting composite

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

**Table 1.4** Examples of the frequency of unwanted placebo/nocebo effects in clinical studies [16]

Nocebo effect	Percentage of incidence of unwanted effects		
	Placebo (P)	Active drug (A)	Difference (A – P)
Headache	32	56	+24
Drowsiness	21	29	+8
Fatigue	30	32	+2
Faintness	6	13	+7
Dizziness	24	50	+26
Nausea	20	30	+10
Vomiting	9	8	-1
Loss of appetite	15	23	+8
Diarrhea	19	15	-4
Abdominal pain	8	17	+9
Anxiety state	25	33	+8
Impaired vision	18	20	+2
Eczema	4	16	+12
Itching	10	16	+6

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 gen-

eral 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 xenobiotic (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.

**TDI:** Tolerable Daily Intake. Daily tolerable intake.

**TWI:** Tolerable Weekly Intake. Weekly tolerable intake.

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