Statement

Suitability of the photoinitiator TPO in dentistry

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Abbreviations

Abbreviation	de	en
2K	Zwei-Komponenten-System	Two-component system
BAPO	Bis(acyl)phosphinoxid	Bis(acyl)phosphine oxide
BPO	Benzoylperoxid	Benzoyl peroxide
CAD/CAM		Computer aided design/computer aided manufacture
CAS		Chemcials Abstract Services
CLP		Classification, labelling and packaging of Substances and Mixtures (1272/2008/EC)
CMR		Cancerogenic, mutagenic or toxic to reproduction
CoRAP		Community rolling action plan
DMAEMA	(2-Dimethylaminoethyl) methacrylat	(2-Dimethylaminoethyl) methacrylate
DNEL		Derived no effect level
EC		European Commission
ECHA		European Chemicals Agency
ED	Endokrine Disruptoren	Endocrine disruptor
ED10		Effective dose (10%)
EDMAB	Ethyl 4-(Dimethylamino)benzoat	Ethyl 4-(dimethylamino)benzoate
GCL		Global classification level
GD		Gestational day
GIC/GIZ	Glas-Ionomer Zement	Glass-ionomer cement
IUPAC		International Union of Pure and Applied Chemistry
KEMI		Swedish Chemicals Agency
Kfo	Kieferorthopädie	Orthodontics
KG	Körpergewicht	Body weight
MAPO		Mono(acyl)phosphine oxide

Abbreviation	de	en
MOD	Mesial-, okklusal-, distale Füllung	Mesial-, occlusal-, distal filling
MOS		Margin of safety
MDR		Medical Device Regulation (2017/745/EC)
NOAEL		No-observed-adverse-effect level
OECD		Organization for Economic Co-operation and Development
OECD TG		OECD test guidelines
PEEK	Polyetheretherketon	Polyetheretherketone
PI	Photoinitiator(en)	Photoinitiator
PMMA	Polymethylmethacrylat	Polymethylmethacrylate
QC		Camphorquinone
QC/Amin		Camphorquinone-amine system
QTH		Quartz tungsten halogen (lamp)
RAC		Risk Assessment Committee
REACH		Registration, Evaluation, Authorisation of Chemicals (1907/2006/EC)
Repr.	reproduktionstoxisch	(Toxic to) reproduction
SCHEER		Scientific Committee on Health, Environmental and Emerging Risks
SCL		Specific concentration limit
SVHC		Substance of very high concern
TPO	Diphenyl-(2,4,6-Trimethylbenzoyl)-Phosphinoxid	Diphenyl-(2,4,6-trimethyl benzoyl)-phosphine oxide
TPO-L	Ethyl (2,4,6-Trimethylbenzoyl) Phenylphosphinat	Ethyl (2,4,6-trimethyl benzoyl) phenylphosphinate

Regulatory situation

Diphenyl-(2,4,6-trimethylbenzoyl)-phosphine oxide (TPO, CAS 75980-60-8) is used in the dental industry in resin mixtures as an initiator for photopolymerisable materials for fabricating, e.g. filling composites, drilling templates, splints, crowns and bridges.

There is a REACH (Registration, Evaluation, Authorisation of Chemicals) registration for TPO and harmonised classification in the CLP regulation (Classification, Labelling and Packaging of Substances and Mixtures, Annex 6).

According to Annex I No. 10.4.1 of the MDR (Medical Device Regulation) the following materials shall only be contained above 0.1% weight by weight (w/w), where justified in persuant to Section 10.4.2 (MDR):

- carcinogenic, mutagenic or toxic to reproduction substance of Category 1A or 1B (CMR substances)
- substances with endocrine disrupting properties […]

This applies to devices, or those parts thereof or those materials used therein that:

- are invasive and come into direct contact with the human body,
- (re)administer medicines, body liquids or other substances, including gases, to/from the body, or
- transport or store such medicines, body fluids or substances, including gases, to be (re)administered to the body.

According to Annex I No. 10.4.2 of the MDR this justification must in particular be the result of an analysis of potential exposure to patients and/or users to the substance, an analysis of possible alternative substances including independent scientific investigations and a reason why possible substitutes with regard to functionality, performance and benefit-risk ratio are inappropriate.

Currently, the CMR classification for TPO is Repr. 2 H361f. However, a substance evaluation under CoRAP (Community rolling action plan) has been carried out by the Swedish Chemical Agency (KEMI) since 2016 with a first update in 2020. This recommends a reclassification of Repr. 2 to Repr. 1B with subsequent labelling as SVHC (substance of very high concern) pursuant to REACH Article 57(c) and, depending on the result of the substance evaluation, also according to Article 57(f). In 2021 an opinion of the Risk Assessment Committee (RAC) was published with regard to this, in which the RAC also came out in favour of classification as Repr. 1B; H360Fd.
Large sections of photopolymerisable composites in dentistry are affected by the forthcoming reclassification (Repr 1B) of TPO..

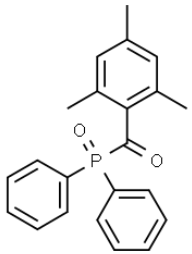
Scope

This document describes TPO and its use in the dental industry. The chemical and biological properties will be described and its suitability for the dental industry presented. Furthermore, alternative materials and treatment methods will be described, including their advantages and disadvantages. The structure of the document is orientated on the EU Guidance Paper of the “Scientific Committee on Health, Environmental and Emerging Risks” (SCHEER) “GUIDELINES on the benefit-risk assessment of the presence of phthalates in certain medical devices covering phthalates which are carcinogenic, mutagenic, toxic to reproduction (CMR) or have endocrine-disrupting (ED) properties“.

Description of diphenyl-(2,4,6-trimethylbenzoyl)phosphine oxide (TPO)

The compound TPO is an organophosphorus substance, which is used in many industrial areas and in the dental industry as a photoinitiator (Table 1). By absorbing electromagnetic radiation this substance forms radicals, which initiate a radical polymerisation reaction. It is available commercially.

Table 1. Characteristics of TPO.

Name (IUPAC)	Diphenyl(2,4,6-trimethylbenzoyl)phosphinoxid (German) Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide (English)
Synonyms	TMDPO; SP-2,4,6; YF-PI TPO; IHT-PI TPO; HRcure-TPO; SPEEDCURE TPO; Photocure TPO; Photoinitiator TPO; Photosensitiser TPO
Molecular formula	$C_{22}H_{21}O_2P$
Structural formula	
CAS	75980-60-8
Molecular weight	348.37 g/mol
Melting point	88 °C – 92 °C
Boiling point	515 °C ± 60 °C
Density	1.218 g/cm^3 at 20 °C

Refractive index	n_{20}/D 1.475	
Flash point	>110 °C	
Stability	Stable, incompatible with strong oxidising agents	
Hazard statements (previous classification)	**H317** May cause an allergic skin reaction **H361** Suspected of damaging fertility or the unborn child **H411** Toxic to aquatic life with long-lasting effects	
Precautionary statements (previous classification)	**P201** Obtain special instructions before use.	
	P202 Do not handle until all safety precautions have been read and understood.	
	P261 Avoid breathing dust.	
	P272 Contaminated work clothing should not be allowed out of the workplace.	
	P273 Avoid release to the environment.	
	P280 Wear protective gloves/protective clothing/eye protection.	
	P391 Collect spillage.	
	P308+P313 IF exposed or concerned: Get medical advice/attention.	
	P405 Store locked up.	
	P501 Dispose of contents/container to ... (refer to manufacturer information on disposal).	

Introduction

Acrylics are organic materials that react first to oligomers and then to polymers (end product) due to a chemical reaction from many subunits (monomers) (1, 2). Monomers with chemically reactive – so-called functional – groups are also required, from which oligomers or polymers can be formed. The functional groups of monomers and initiator system determine the type of polymerisation reaction. The subdivision of polymerisation reactions takes into account the kinetic process; here it is differentiated between (i) step-growth reactions and (ii) chain-growth reactions.

(i) Step-growth reactions

- **Polycondensation**: Formation of polycondensates under separation of mainly water. Typical examples for polycondensates include polyethers, polyesters and polyamides.
- **Polyaddition**: Formation of polymers, without separation of by-products.

(ii) Chain growth reactions

- **Radical polymerisation:** Radical initiated reactions are generally mainly subdivided into three substeps. In the first substep the radical is formed (initiation), in the second propagation (chain growth) takes place and in the third termination (chain termination). Typical radical formers include the thermal initiator benzoyl peroxide, azobis(isobutyronitrile) and the photochemical initiator TPO.
- **Cationic/anionic polymerisation:** Brønsted acids (proton donors) and Lewis acids (electron pair acceptors) are used as initiators during cationic polymerisation. The propagating polymer therefore has a positive charge and is consequently present as a cation. The counterpart to cationic polymerisation is anionic polymerisation. In this case Brønsted bases (photon acceptors) and Lewis bases (electron pair donors) are used. The propagating chain therefore has a negative charge and is consequently present as an anion. There is also photochemically initiated polymerisation using sulfonium and iodonium salts.
- **Coordination polymerisation:** Polymerisation mainly using transition metal complexes. Monomers, oligomers and polymers coordinate at the transition metal complex; through for example insertion, another monomer unit bonds to the oligomer or polymer from the transition metal complex.

From the types of reaction cited above, radical polymerisation has the greatest significance in dentistry. Composites (filling-, veneering-, framework- and luting-resins, adhesives etc.) and denture acrylics react in radical polymerisation to produce the end product. Initiation of radical polymerisation is induced by decomposition of an initiator. The initiator can decompose under the formation of two or more radicals by adding energy (e.g. heat and/or light). The resulting radicals then initiate the start of the chain reaction and chain growth. The initiator radical can, e.g. react with the carbon-carbon double bond of monomers. The result of this is a radical, from which an initiator radical extended by one monomer unit is created. These

radicals now react successively with other monomers, initially forming oligomers and ultimately polymers. Termination of the polymer radicals can occur by recombination of two radicals or disproportionation reaction, whereby further propagation of the polymer is inhibited. The initiator is activated by the addition of energy, as stated at the beginning. Different sources of energy can be used for this, which are selected according to the requirements of the processing procedures in dental technology and dentistry.

- **Heat-curing, heat polymerising systems**: in this case the energy is used in the form of heat, e.g. by using water tanks. Application: denture acrylics.
- **Photocuring, photopolymerisation systems**: in this case the energy is introduced in the form of electromagnetic radiation. Two wavelengths are primarily used in dentistry: approx. 385 nm (near UV radiation) or 400 to 420 nm (blue light).
- **Chemically curing, cold-curing, chemically polymerising, cold-polymerising, autopolymerising systems**: in this case the energy is supplied by a chemical reaction between the initiator and another substance (= accelerator).

All of these systems are based on radical polymerisation, which requires the presence of initiators. The choice of initiator system depends on different process parameters. Coordinated process parameters will be discussed in more detail the following sections.
The exchange of initiators is possible under certain conditions, but can result in limitations in processing or deviations with the product properties. Type and concentration of the initiator, physical-chemical properties of the monomers used and other process parameters can influence the polymerisation to a significant extent. A more rapid and complete substance conversion of monomers and initiator system is aimed at during polymerisation. TPO has proven successful in photocuring systems based on its beneficial properties as initiator and is therefore used in a large number of dental products.

Alternative treatment methods and materials

Alternative treatment methods

Photopolymerisable composites are produced for the fabrication of different types of dental restorations. Composites and in particular photopolymerisable composites have become established as an important material group in dentistry for a large number of indications. They have become successful for use in many forms of treatment due to their good material properties and user-friendly handling or processing. They can be processed using not only conventional procedures but also additive (3D printing) or subtractive (milling, CAD/CAM) procedures. Thanks to their CAD/CAM capability, e.g. new treatment options have been developed such as aligner therapy. Table 2 compares forms of treatment based on products containing TPO to possible alternatives.

Table 2. List of different forms of treatment and possible alternatives. Note: this table is non-exhaustive.
* contains, e.g. strength and abrasion resistance

Form of treatment	Form of treatment containing TPO	TPO-free form of treatment / alternative materials	Evaluation of the alternative (TPO-free) forms of treatment compared with the forms of treatment containing TPO
Filling treatment	Direct fillings	Amalgams	• (+) Lower aesthetics • (+) More invasive (preparations only with undercut) • (+) Higher ecotoxicity (environmental pollution by mercury) • (-) Easier processing • (-) Longer service life* • (-) Lower treatment costs
		Gold leaf	• (+) Lower aesthetics • (+) More time-consuming processing • (+) Higher treatment costs • (-) Longer service life*
		Cements (GIZ)	• (+) Lower aesthetics • (+) Lower strength • (-) Easier processing • (-) Remineralisation possible + • (+) Shorter service life
		TPO-free composite filling materials	• Comparable aesthetics • Comparable strength • Comparable processing • Comparable service life • Comparable treatment costs
	Indirect fillings (inlay, onlay, veneer)	Ceramics, glass-ceramics, PMMA PEEK	• Comparable aesthetics • Comparable strength

			• Comparable processing • Comparable service life • Comparable treatment costs • (-) More abrasion resistant +/- antagonist abrasion
		Metals	• (+) Lower aesthetics • Comparable strength • Comparable processing • (-) Longer service lift, but (+) antagonist abrasion possible Comparable treatment costs
Dental restorations	Crowns and bridges Veneering materials	PMMA, composite veneered metals	• Comparable aesthetics • Comparable strength • Comparable processing • Comparable service life • Comparable treatment costs
		Unveneered metals	• (+) Lower aesthetics • Comparable strength • Comparable processing • Comparable service life • Comparable treatment costs
		Ceramics, glass ceramics	• Comparable aesthetics • Comparable strength • Comparable processing • Comparable service life • Comparable treatment costs
	Luting materials incl. adhesives	2K / dual-curing composites Other UV-curing composites (e.g. CQ) Cements	• Comparable aesthetics • Comparable processing • Comparable service life
	Denture lacquer	CQ-based, PMMA	• Comparable aesthetics • Comparable strength • Comparable processing • Comparable service life

			• Comparable treatment costs
	Veneering materials	Ceramic	• Comparable aesthetics • Comparable strength • Comparable processing • Comparable service life • Comparable treatment costs • (-) More abrasion resistant +/- antagonist abrasion
		TPO-free composites	• Comparable aesthetics • Comparable strength • Comparable processing • Comparable service life • Comparable treatment costs • (-) More abrasion resistant +/- antagonist abrasion
	Denture teeth	Ceramic	• Comparable aesthetics • Comparable strength • Comparable processing • Comparable service life • Comparable treatment costs • (-) More abrasion resistant +/- antagonist abrasion
		PMMA	• Comparable aesthetics • Comparable strength • Comparable processing • Comparable service life • Comparable treatment costs
	Denture base	PEEK, nylon, chemically curing denture acrylics	• Comparable aesthetics • Comparable strength • Comparable processing • Comparable service life • Comparable treatment costs
Prevention	Fissure sealer	TPO-free composite filling materials	• Comparable aesthetics • Comparable strength • Comparable processing

			• Comparable service life • Comparable treatment costs
Orthodontics	Splints for orthodontics	Restoration of older technical units (wires /brackets etc.)	• (+) Lower aesthetics • (-) Lower treatment costs • (+) More time-consuming processing • (-) Higher treatment adherence (children/adolescents) • (+) Increased risks of enamel damage when detaching the brackets
		Vacuum-formed templates	• Comparable aesthetics • Comparable strength • Comparable processing • Comparable treatment costs
Drilling templates	General templates	PMMA	• Comparable effort • Comparable costs

As some indications can also be covered by 3D printed materials, these fabrication methods should be considered separately. If composites are fabricated additively, in most cases formulations containing TPO are used**.** In addition to the necessary compatibility with the light sources of commercially available 3D printers (absorption range) and a high efficacy of the photochemical initiation, TPO also has a relatively low impact on the colouring of the end product in comparison with chemically related BAPO. TPO has better solubility than BAPO in the most widely used monomers, which is significant for the fabrication of photopolymerisable resins. As a liquid PI, TPO-L is even easier to use but in contrast to TPO and BAPO it has a considerably lower absorption and efficacy during initiation, which can have a negative effect on the required fabrication time of the dental product. Overall, TPO has therefore balanced substance and application properties, which explains its widespread use in photocurable compositions.
3D printing covers a wide range of indications (crowns, bridges, inlays and onlays), allowing their fabrication directly in the dental laboratory. For 3D printed partial crowns and laminate veneers to preserve the original tooth, it does not have to be reduced or reduced only very slightly, as in this case more accurate fabrication is possible (keyword nonprep). Moreover, treatment can be completed chairside in one appointment; repeated anaesthetising of the patient can be avoided, as occurs with all chairside procedures (SLM [selective laser melting] procedures (metals), milling of composite, glass ceramic and ceramic/zirconia). In this case the advantages and disadvantages analogous to Table 2 should be considered. The special characteristics of composites fabricated additively, however, are the diverse, quick and cost-effective treatment possibilities.
The alternative treatments named in Table 2 with their advantages and disadvantages should not be regarded as recommendations of the manufacturer, but should only serve as a guide for deciding on a specific material. This decision is always made by the treating dentist in consultation with the patient, whereby practical considerations such as financing, treatment duration and aesthetics can play a role. It is the aim of the manufacturer to be able to make the suitable material available for every patient situation.

In addition to the use of direct filling materials, luting composites and adhesives would also be affected by the replacement of TPO. This is guaranteed with the help of light-curing or dual-curing luting composites.

Alternative initiators

The following general requirements should be placed on PIs:

- Compatibility between absorption characteristics of the PIs and emission characteristics of the light source
- High light yield
- High solubility in the polymer and for biomedical application a high water solubility
- Non-cytotoxic
- No yellow discoloration of the cured product
- Thermal and temporal stability

Camphorquinone (CQ) and its derivatives, in combination with amine synergists and phosphine oxides are by far the most widely used PIs in dentistry. In the following sections the properties as well as advantages and disadvantages of CQ/amine systems and phosphine will be examined in greater detail.

Chemical properties of TPO

This section is intended to provide a general overview about the chemistry of light-curing composite. The focus here is on the properties of TPO. For better understanding of the interrelationships, firstly the fundamentals of the photoinitiated polymerisation reaction will be presented. The subsequent section goes into greater detail about TPO and related PIs.
Further background information regarding selection of a PI is collected in Annex A. This includes possible competitive or side reactions of the radicals formed as well as factors, which have an influence on the selection of the PI system.

General chemistry and function of PIs

The resin base usually consists of linear organic molecules with one or more terminal acrylate or methacrylate groups, the monomers or oligomers. During polymerisation they are linked to polymers, which proceeds over the three principle polymerisation steps: chain -start, -growth and -termination. PIs are molecules that have suitable molecular structures to absorb energy from photons (light energy) and to transform into chemical energy in the form of reactive radicals, which for their part initiate the polymerisation reaction. The light absorbing part of the molecule or chromophore is linked with the radical-forming part. The light absorption triggers a chain of processes in the electron shell of the photoinitiator molecules: the ground state transforms to a high-energy, excited state (PI* singlet), which ultimately generates radicals over another excited state (PI* triplet):

PI (ground state) + UV -> PI* (singlet) -> PI* (triplet) -> radicals

It should be mentioned that the energy of the UV or visible light is in the 70 to 80 kcal/mol range. This energy is available for splitting the chemical bond in the PI molecule under radical formation, which should be taken into consideration when selecting suitable molecular structures.
The process described is called Type 1 or Norrish Type 2, which is further subdivided into alpha and beta fissions. Alpha fissions include fission of the bond at the so-called alpha-carbon atom of the initiator molecule, while the more seldom occurring beta fissions take place at weak bonds of the carbon atom in alpha-position to a heteroatom (e.g. C-Cl, C-S or C-N). All fissions mentioned so far take place monomolecular, which means it is only the initiator molecule itself that is involved in the reaction.
Furthermore, there are Norrish Type 2 initiators, in which the PI does not split following light absorption but reacts in the high-energy triplet state with a suitable hydrogen donor (synergists). As two separate types of molecules are involved in this mechanism, it is a bimolecular mechanism. Suitable synergists include tertiary amines, ethers, esters or thiols, which carry activated hydrogen atoms in the alpha-carbon position to the heteroatom. The PI triplet state can abstract this hydrogen atom; the end products of such a reaction are a so-called ketyl radicals with relatively low reactivity and a donor radical with high reactivity, which start polymerisation.

PI* (triplet) +HD (donor) -> PI·H (ketyl radical) + D· (donor radical)

Both reaction pathways (Type 1 and Type 2) will be discussed in more detail in the respective subsections about PIs.

As the triplet state of the Pis is a high-energy transition state, it can return to the more low-energy ground state under energy transfer in the form of light or, in addition to the required radical formation, undergo other reactions.
Other deactivation processes such as quenching by monomers or oxygen can also take place. The lifespan of the triplet states with Type 1 Pis is very short before splitting, competitive quenching processes therefore do not have too great an influence on the reaction event. Type 2 Pis in contrast have longer triplet lifespans, which though it allows time for the reaction with hydrogen donors, it also increases the likelihood of quenching reactions (Figure 1).

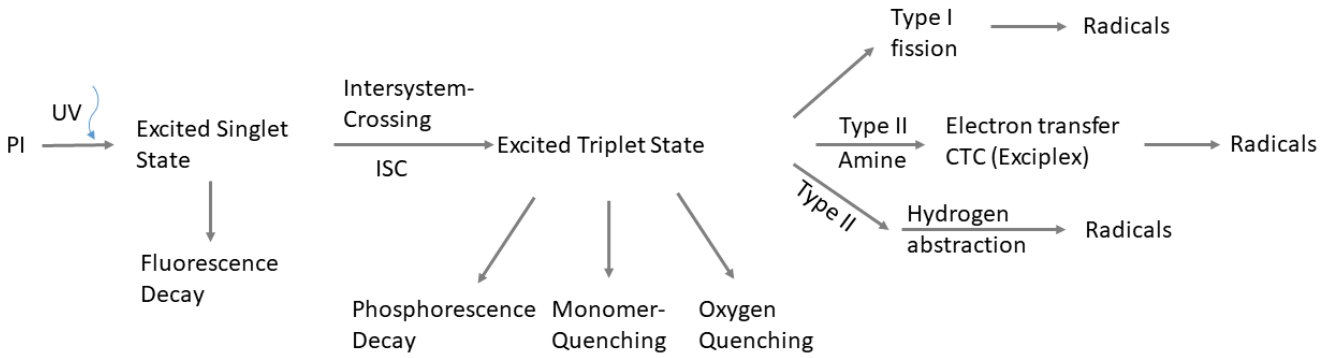


Fig. 1: Reactivating and deactivating processes during formation of radicals (adapted from [1]).

Polymerisation and side reactions

The free radicals formed at the beginning of the curing process are required for initiation of the polymerisation process of monomers and oligomers. As soon as a radical is created, it reacts with a monomer under formation of a monomer radical. The subsequent initiated chain growth ultimately results in polymers. Provided further radicals are produced, chain growth is the main reaction pathway. In addition to the quenching reactions already

mentioned, radicals can be subjected to other side reactions – some of which are deactivating, others are photochemical and thermal side reactions – which can result in a range of by-products. These side reactions will be assessed separately in Annex A.

Phosphine oxides

Phosphine oxides were developed from the esters of acyl phosphonic acids, which initially had very weak photoinitiating properties. Phosphine oxides absorb in a narrow band in the long wave UV range (350-420) nm. Thanks to their photobleaching properties, they make it possible to cure to a good depth by absorbing light less strongly with progressive polymerisation and enabling a higher penetration depth of the light. Though phosphine oxides are intrinsically coloured yellow as a result of the position of the absorption bands, photobleaching enables the manufacture of whiter composites. Because of their high efficiency phosphine oxides are used in a large number of photocurable compositions such as printing inks or coatings. The phosphine oxides TPO, TPO-L and BAPO shown in Figure 2 have established a wide range of uses.

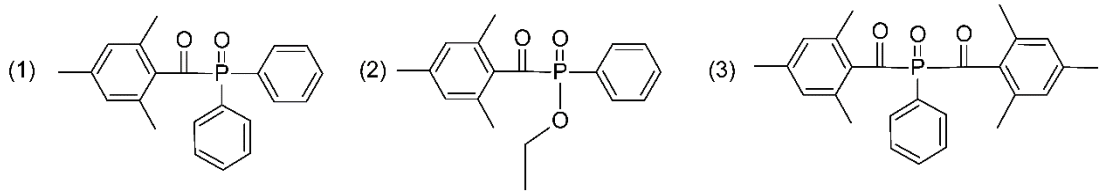


Fig. 2. Structural formulae of TPO (1), TPO-L (2) and BAPO (3).

The molecule structures shown have been optimised towardsa good shelf-life (chemical stability) and high efficiency of transformation of light energy into radicals (quantum yield).

After alpha fission of TPO, a trimethylbenzoyl radical and a phosphinoyl radical are obtained:

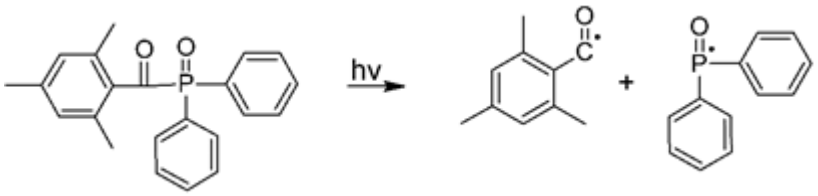


Fig. 3. Reaction scheme for the creation of radicals from TPO. Homolytic splitting takes place at the C-P bond, whereby the starter radicals are formed. Both radicals generated in this way are capable of starting radical polymerisation with different conversion rates, respectively.

Both radicals generated in this way are capable of initiating polymerisation of monomers and oligomers, which results in polymer chains with phosphinoyl or trimethylbenzoyl groups on their end:

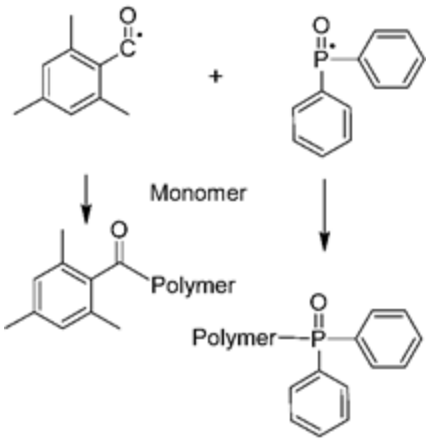


Fig. 4. Termination of the polymer chains formed by TPO fragments.

TPO is the most frequently used phosphine oxide-based PI, which (as a crystalline powder) is highly soluble in most monomers and combines excellent absorption properties and quantum yields. TPO-L (Ethyl-(2,4,6-trimethylbenzoyl)phenylphosphinate), in contrast, is a liquid that can be easily mixed in formulations but has a lower absorption, which manifests itself in a lower reactivity despite a higher quantum yield.

BAPO (Phenyl-bis-(2,4,6-trimethylbenzoyl)phosphine oxide), on the other hand, has a considerably stronger absorption than TPO in the long wave UV range (1200 vs. 610 $l \cdot mol^{-1} \cdot cm^{-1}$ at λ_{max}) and also has a quantum yield almost twice as high. These properties are the result of the molecular structure: Instead of two radicals, BAPO is theoretically capable of producing 4 radicals (Figure 5). Following the first fission, a Trimethylbenzoyl radical and a Trimethylbenzoyl phosphinoyl radical are formed, both of which are reactive. The latter radical can be split further, resulting in a second Trimethylbenzoyl radical and a (monomer)-phosphinoyl radical. Due to the strong absorption in the visible spectrum BAPO is predestined for curing pigmented composites, as it has a superior penetration capability compared with the UV range longer wave radiation. The increased number of reactive radicals ensures quick, efficient curing.

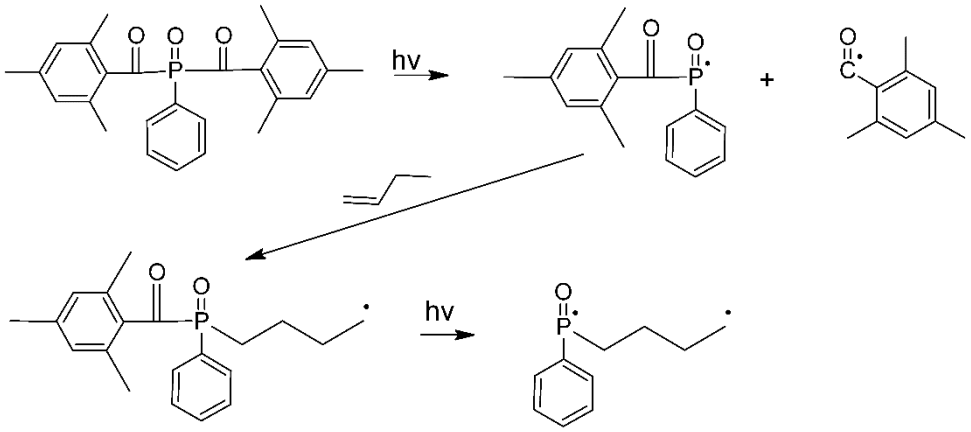


Fig. 5: Stepwise alpha splitting of bisacylphosphine oxides.

Phosphine oxides do not require synergists or Co-Initiators, which can often have a negative impact on product properties, e.g. color stability. They are particularly suitable for quick curing of higher layer thicknesses, which has a beneficial effect on applications such as materials for dental fillings. In combination with modern light sources, e.g. LEDs, phosphine oxides are an efficient group of PIs, which are state-of-the-art in dentistry.

Summary

It is clear from the preceding explanations and additional information given in Annex A, B and C that photocurable dental materials are complex systems. The interplay of the individual components and the selection of suitable processing parameters enable reliable use by dental technicians or dentists.

Furthermore, there are also aesthetic requirements that these materials must meet. Consequently, during material development a range of important, sometimes interdependent factors must be taken into account:

- The monomers and oligomers used, the number of polymerizable groups per molecule
- Inorganic filler material and their effect on the PI system
- Particle size and particle size distribution of the filler material. Light scatter through the pigment particles can have a significant impact on polymerisation. They can also have an influence on the rheology (flow behaviour) and sedimentation (settling behaviour).

- Colour stability
- Solubility of the PI in the mixture
- The film thickness and required curing speed
- Relative costs of the initiators
- Specific lamp emissions and respective radiation power
- Yellowing effects during and after curing
- Toxicity of the components and labelling with regard to sensitive applications

These factors must be harmonised, to ensure that the technical requirements, the criteria for product safety, and costs are met. New developments of key components such as PIs are time-consuming and generally cause higher costs.

Optimisation of dental materials in the last decade has led to the products available today, which are state-of-the-art in terms of their mechanical and aesthetic properties as well as their handling, including short processing times. The intrinsic polymerisation shrinkage that occurs during light curing has been reduced and can be controlled to the extent that application is possible without any problem. The abrasion characteristics could also be improved. Last but not least, development of LED technology and consequently the availability of suitable light sources played a major role in establishing photocurable dental materials.

Toxicological properties of TOP and alternative substances

This section is intended to provide an overview of the toxicological effects of TPO, together with an evaluation of possible alternative substances. First, the available toxicity data of TPO will be reviewed and then CQ together with the most commonly used amines DMAEMA and EDMAB will be discussed.

To determine the amount of leachable PI, extraction studies pursuant to EN ISO 10993-18 were carried out by the manufacturers involved in this statement. This data collection represents a broad range of different extraction parameters (time, polarity of the solvent, temperature etc.).

The toxicological profiles of by-products were not evaluated separately.

Review of toxicological data of TPO

Excerpts from the RAC statement on diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide (TPO)

"For the safety assessment of diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide three studies on reproductive toxicity were carried out by the registrants: (...)

1. an oral reproductive/developmental toxicity screening test according to OECD TG 421 on rats:

TPO in doses of 0, 60, 200 and 600 mg/kg body weight (bw)/day was administered orally to ten Wistar rats per gender and group (Study report, 2019) (...)

2. one oral prenatal developmental toxicity study (OECD TG 414) in rat:

administered by gavage to 22 mated, female Wistar rats per group at dose levels of 0, 50, 150 and 500 mg/kg bw/day (Gestation Day) (GD) 6-20) (Study report, 2016) (...)

3. one oral prenatal developmental toxicity study (OECD TG 414) in rabbit:

administered by gavage to 22 mated female New Zealand rabbits per dose group of 0, 10, 30 and 100 mg/kg bw/day on gestation day (GD) 6-28 (Study report, 2018) (...)"

Mainly based on these 3 studies the RAC (Risk Assessment Committee) came to the following conclusion in relation to the classification of TPO with regard to different reproductive endpoints:

Adverse effects on the sexual function and fertility:

“In summary, (…). In more recent oral reproductive/developmental toxicity screening test pursuant to OECD TG 421 (Study report, 2019) with doses up to 600 mg/kg bw/day, adverse effects were observed on testis and epididymides was observed in the absence of marked general toxicity. The fertility index in the high-dose group of 600 mg/kg bw/day was at 0% and all males in this dose group showed massive tubular atrophy in the testes and reduced luminal sperm with luminal cell debris in the epididymes.

Overall, classification as Repr. 1B for adverse effects on sexual function and fertility is appropriate based on clear evidence of adverse effects on testes and epididymes, in the absence of a marked general toxicity, which lead to a reduction of fertility. In conclusion, the RAC considers that classification of TPO as Repr. 1B; H360F is justified.“

Adverse effects on development:

“In summary, the developmental toxicity study in rats is relevant for a classification for adverse effects on development based on the finding of skeletal malformations including bent limb bones and the statistically significant increased incidences of skeletal variations, including bent ribs, reduction in ossification of skull bones and unossified metatarsals and/or metacarpals in the high dose group which were outside historical control data, and observed in the absence of marked maternal toxicity. RAC notes that the developmental toxicity study in rabbits did not show any effects relevant for classification, however, the tested doses were considered not sufficiently high to cause treatment related general toxicity in the maternal animals. Furthermore, in the OECD TG 421 screening test in rats, where no females were pregnant at 600 mg/kg bw/day, the highest dose for assessment of developmental findings was the mid dose of 200 mg/kg bw/day which limits the assessment for developmental toxicity. The only developmental effect observed was a dose related, however, not statistically significant increase in anogenital distance.

Overall, a classification as Repr. 2 for adverse effects on development is appropriate based on some evidence of adverse effects including increased incidence of skeletal malformations and variations in rats, in the absence of marked general toxicity. RAC considers that a classification of TPO as Repr. 2; H361d is justified.” (…)

Overall classification conclusion

“In conclusion, RAC is of the opinion that TPO warrants classification as Repr. 1B; H360Fd” (…)

“The ED10-values based on the effects on fertility and reproductive organs observed In the OECD TG 421 study in rats (Study report, 2019). For fertility index an interpolation between the NOAEL (100% at 200 mg/kg bw/day) and LOAEL (0% at 600 mg/kg bw/day) results in a ED10 of 240 mg/kg bw/day based on the following calculation:

(600-200) / (100-0) = 4.0 mg/kg per % (steepness). Going from 100% to 90% requires subtraction of 10%. This equals 10% x 4.0 mg/kg per % = 40 plus 200 as the starting point = 240 mg/kg bw/day.
The ED10-values all fall within the medium potency group (4 mg/kg bw/day < ED10-value < 400 mg/kg/bw/day), and hence for a classification in category 1B for adverse effects on sexual function and fertility, the GCL (Global Classification Level) of 0.3% should apply.

Modifying factors are not considered relevant to apply in this case since the calculated ED10-values are not borderline to a higher or lower potency group.

Overall, RAC is of the opinion that no SCL is appropriate based on the ED10 values calculated, and the GCL should apply.”

Conclusion for the labelling of medical devices

Respective naming of TPO in safety data sheets and consecutive CLP Labelling requirements are only mandatory from 0.3% in the chemical mixture. Labelling is necessary for products utilized in the dental laboratory, which are not used in direct contact with the patient.

According to the Medical Devices Regulation (Annex 1, Chapter 11 10.4 ff,), from 0.1% TPO in the chemical mixture corresponding risk assessments and labelling obligations according to ISO 15223 are required .

Considerations for exemplary calculation of safety margins for dental medical devices

For the key reproductive toxicity study OECD 421 in rats the companies, who registered the substance TPO, reached the following conclusion in the registration dossier (as published on the ECHA homepage):

“In conclusion, based on the results of this reproduction/developmental toxicity screening test, the following no-observed-adverse-effect level (NOAEL) of Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide were established:

Parental NOAEL: 200 mg/kg (Based on clinical signs and reduced body weight gain (males).)

Reproduction NOAEL: 60 mg/kg (Based on adverse microscopic findings in the male reproductive organs at 200 and 600 mg/kg.) (Based on the low mating and fertility index at 600 mg/kg.)

Developmental NOAEL: 200 mg/kg (no data available at 600 mg/kg)."

RAC assessed the NOAEL for the toxicological endpoint fertility at 200 mg/kg bw/day, based on functional findings/fertility index determined in the OECD 421 in rats. This is in contrast to the registrants, who determined the reproductive NOAEL as being 60 mg/kg bw/day based on the microscopic findings.

For margin of safety calculations in the toxicological risk assessment of TPO in dental medical devices the lower NOAEL of 60 mg/kg bw/day was used as a safety measure and conservative approach. Safety factors of 10 each for the inter- and intra-species extrapolation were applied for calculations. An additional safety factor of between 1 and 10 for uncertainties in the study designs as such were not applied due to the more

conservative approach in choosing the NOAEL. This type of study-dependent uncertainty factor was not even used by the RAC in the ED10 assessment.

In the original REACH registration dossier there was a **DNEL** (Derived No Effect Level – derived value in which no effects are expected with a daily intake) of **83.3 µg/kg bw/day** for oral intake based on a sub-chronic oral toxicity study in rats in which a **NOAEL of 50 mg/kg bw/day** was determined. A DNEL was then derived with a total factor of 600. Whether this DNEL will be changed based on the new study situation, is not yet clear at this point in time. Consequently, the exposure scenarios will also be calculated with the DNEL.

The MDR requires the safety assessment of particularly vulnerable groups such as children, pregnant and breastfeeding women.

For TPO in dental medical devices children and pregnant women were identified as such a risk group based on the toxicological endpoints determined. For exemplary calculations children with a body weight of 10 kg were assumed based on ISO 10993 Part 17, though dental treatment of children only starts with children at a higher age and consequently a higher body weight. Assumption of a body weight of only 10 kg therefore provides an additional safety level.

For the vulnerable group of pregnant women the average body weight of women was used pursuant to ISO 10993 Part 17 (58 kg). An additional layer of safety is given, sincethe evidence of developmental toxicity was not considered as robust as for fertility, which is reflected in the classification as Class 2 developmental toxicant. Further, the NOAELs are of the developmental endpoint is higher than that of the reproductive/fertility endpoint.

However, the unborn male child should be considered and thus to exclude intra-uterine damage an additional safety factor of 10 can be applied.

Breastfeeding is not considered a specific vulnerable group according to the RAC opinion, no classification took place, thus the NOAELs for fertility should lead to a sufficient safety level.

Based on the lowest existing NOAEL for reproductive toxicity of 60 mg/kg bw/day, using the safety factors for the inter- and intra-species extrapolation as well as for intrauterine damage of male offsprings (10 each) a very conservative DNEL of 60 µg/ kg bw/day is estimated for the subsequent calculations of the safety margins, which is even lower than the DNEL of 83.3 µg/kg bw/day previously proposed by REACH**.**

References

Committee for Risk Assessment RAC Opinion proposing harmonised classification and labelling at EU level of diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide EC Number: 278-355-8 CAS Number: 75980-60-8 CLH-O-0000007023-85-01/F Adopted 16 September 2021

Committee for Risk Assessment RAC Annex 1 Background document to the Opinion proposing harmonised classification and labelling at EU level of diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide EC Number: 278-355-8 CAS Number: 75980-60-8 CLH-O-0000007023-85-01/F (Adopted 16 September 2021)

Toxicological information endpoint summary Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide EC number: 278-355-8 | CAS number: 75980-60-8

ECHA Database

ISO 10993 Standards (in the most currentversion)

ISO 15223 (in the most currentversion)

Toxicology of camphorquinone (CAS 10373- 78-1 / CAS 10334- 26-6)

This substance is a low tonnage material (according to REACH < 10t/a). Toxicological studies into specific endpoints (e.g. reproductive toxicity) must not be carried out for this tonnage band.

Racemic camphorquinone has been classified by REACH registrants as irritating to skin, eyes and airways. Pure 1R camphorquinone is also classified as acute toxic Cat 4.
There is evidence from model calculations that the substance may also have a certain reproductive toxicity. Experimental data that prove or devalidate this presumption are not available to us. A classification has not been proposed by the chemical agency to date. Corresponding toxicological animal tests are not required by the respective raw material manufacturers or importers in the EU due to the low yearly production quantity.

Reference: ECHA database / CAS 10373- 78-1 / CAS 10334- 26-6

Toxicology of DMAEMA (CAS 2867-47-2)

This substance is registered pursuant to REACH regulation and is manufactured and/or imported in the European Economic Area in a quantity of ≥ 1,000 tons per year

According to the REACH registration dossier no **DNEL** (Derived No Effect Level – derived daily amount without toxicological effect) was determined for the general population for oral uptake, **as the substance only exhibited very low toxicity.**

For dermal exposure DNELs were derived for the systemic effect of 25 mg/kg bw/day. For the local effect a DNEL of 125 mg/kg bw/per day was derived.

Reference: ECHA database / CAS 2867-47-2

Toxicology of EDMAB (CAS 10287-53-3)

This substance is registered pursuant to REACH regulation and is manufactured and/or imported in the European Economic Area in a quantity of ≥ 10,000 to < 100,000 tons per year.

According to the REACH registration dossier a **DNEL** (Derived No Effect Level – derived daily amount without toxicological effect) of **80 µg/kg bw/day** was determined for the general population for oral uptake based on effects on the fertility.
The NOAEL (No Adverse Effect Level – dose without observed adverse effects) was determined in a subacute oral toxicity study in rats with 40 mg/kg bw/day for developmental toxicological effects, and with 50 mg/kg bw/day for effects on fertility.

Reference: ECHA database / CAS 10287-53-3

Exposure scenarios for dental products containing TPO

Due to the diverse application possibilities of dental materials at this point all possible exposure scenarios for products containing TPO cannot be evaluated, but only exemplary data sets from authors of this statement are evaluated. Two products are examined as an example for materials containing TPO. Drilling guides are used as an example for brief contact and temporary crowns and bridges have been used as an example for medium to long-term contact. All products were examined for TPO content in the extracts by the respective manufacturers in different extraction studies based on EN ISO 10993-12.
The following data were compared for this:
i) uncured: the TPO content in the resin mixture (resin for printing), in relation to the total weight of the product, and
ii) cured: extraction data on final, fully cured products.
As can be seen from Table 3, the MOS for the resin mixture (uncured) was compared with the cured product. This was assessed separately for children, men and women. The result shows that the cured product (green) in contrast to the uncured resin solution (red) can be classified as safe.

Table 3. Comparison of the TPO content (in uncured vs. cured state) to the toxicological threshold limit values

Test article: Drilling template		**~45 cm²**		**5.21g**					
Extraction under simulated conditions: 3 cm²/ml, 37C° ± 2°C, 72 h, methanol									
Quantity [µg/device][a]		**Assumed body weight (pursuant to ISO 10993-17)**		**Maximum permitted dose [DNEL]**		**Margin of safety (MOS)[b]**		**Acceptable (MoS>1)**	
Uncured	Cured	Person	bw [kg][d]	µg/kg bw/day	µg/d[e]	Uncured	Cured	Uncured	Cured
104 200	76.7	Child	10	60	300	0.005	1.3	No	Yes
104 200	76.7	Man	70	60	2100	0.04	9	No	Yes
104 200	76.7	Woman	58	60	1740	0.03	7.5	No	Yes

Test article: Temporary crowns and bridges	**~69 cm²**	0.507g (anterior tooth); 0.765g (posterior tooth) 20 teeth in the deciduous dentition. 32 teeth in adults
Extraction under simulated conditions: 3 cm²/ml, 37 C° ± 2 °C, 72 h, methanol		

Quantity [µg/device][a,c]		Assumed body weight (pursuant to ISO 10993-17)		Maximum permitted dose [DNEL]		Margin of safety (MOS)[b]		Acceptable (MoS>1)	
Uncured	Cured	Person	bw [kg][d]	µg/kg bw/day	µg/d[e]	Uncured	Cured	Uncured	Cured
184 000	0.08	Child	10	60	300	0.003	1250	No	Yes
294 000	0.13	Man	70	60	2100	0.014	8750	No	Yes
294 000	0.13	Woman	58	60	1740	0.011	7250	No	Yes

[a] These values have either been derived from the TPO content of the resin mixture or from data of the respective extraction.
[b]The margin of safety (safety quantity) is determined as the ratio from the threshold limit value and the actual exposure and used in the evaluation. An MOS value greater than 1 usually means that in all likelihood there are no adverse effects on humans. The values have been rounded off to depict a worst-case scenario. Note: ISO 10993-18 requires that in the framework of chemical characterisation analytical data should also be checked for possible uncertainties, as required. In Annex E, this standard recommends the use of an uncertainty factor UF = 2 for chromatographic determinations. If another variation of extraction of ± 50% is assumed, which corresponds to an uncertainty factor UF = 1.5, the result is a total UF of 3 for the extraction data. The margin of safety (MOS) was therefore calculated as a ratio of the DNEL and the analytically determined extraction value *3.
[c] The surface of 69 cm² corresponds to 32 teeth, the factor 20/32=0.625 was used for calculation of the surface of the deciduous dentition.
[d]BW: Body weight
[e]d = day

Firstly, it is noticeable when looking at the collected data in the table that with the two indications the DNEL of 60 µg/kg bw/day falls short for the uncured material. In this case it is clear that for these materials, it is important that they are fully cured according to the manufacturer's instructions for use.

Drilling templates

To estimate the exposure of TPO from drilling templates, different extractions were performed under **simulated conditions** (37°C, 72 h, MeOH). The highest eluted quantity during extraction was 1.7 µg/cm². With a worst-case scenario surface area of 45 cm² this corresponds to 76.7 µg/device, which falls below the DNEL even for low body weights, e.g. children.

Temporary crown and bridge material

To estimate the exposure of TPO from temporary crowns and bridges, different extractions were performed under **simulated conditions** (37°C, 72 h, MeOH or H_2O). The highest eluted quantity during extraction was 1.8 ng/cm² (in MeOH). In H_2O no TPO could be detected within the measurement sensitivity. With a worst-case surface of 69 cm² (32 crowns) this corresponds to 0.13 µg/device, which falls well below the DNEL (MOS≥1250).

It is clear from the collected data that curing of the materials play a significant role: If the materials are not correctly cured in accordance with their prescribed instructions for use, exposure of TPO can exceed the toxicological threshold limit values. In contrast, if the materials are cured in accordance with the IFU of the respective manufacturer and material, the margins of safety (MOS) are in the four- to five-figure range, even taking the uncertainty factors cited in the previous section into account t c.
Due to the complexity of such investigations and the corresponding evaluation all indications cannot be covered in this document. Every manufacturer has the duty to prove the safety of their products. At this juncture, references should be made to the technical documentation of the respective product for this.

Adhesive and composite

The examples shown at the beginning of this section are examples of products cured outside the patient's body.
However, TPO is also used in dental adhesive and composite systems as a PI in an initial concentration of 2% or 0.1% in the product. These products are cured intraorally, which is why they will be considered separately in this section.
Assuming a large MOD filling, a product usage of 4 mg (bonder) or 220 mg (composite) is expected. Assuming (worst case) simultaneous treatment of 3 teeth and no chemical conversion/consumption of TPO, there is a total exposure of 240 µg or 660 µg TPO from adhesive and composite, respectively.

Assuming that the general DNEL for oral uptake and the general population of 60 µg/kg bw/day applies, this results in tolerable daily uptakes of TPO for men of 4.2 mg/day and for women of 3.4 mg/day. In relation to the assumption cited above of a one-off maximum dose of TPO by an adhesive and composite cavityfilling system, there is still a safety margin of 3-4 times dose of the DNEL.
For children smaller fillings can be assumed in the deciduous dentition, so that a safety margin of 1 is also presumed for this extreme case.
Additional safety factors result from the frequency of exposure (these do not occur repeatedly on a daily basis with a composite filling). For the worst-case scenario it was also assumed that there was no chemical conversion and a one-off release of the total quantity of TPO on the first day of exposure. In reality a chemical conversion of the substance and release of existing residual quantities over a longer period will take place. The daily doses of TPO are consequently lower than in the case described above.
It can therefore be concluded that the use of TPO in a concentration of 2% or 0.1% in an adhesive-composite cavityfilling system can be considered acceptable and safe with regard to reproductive toxicological effects.

Summary

- As is evident from Table 3,a crucial factor for a safety of the custom-made device is the preceded manufacturing according to the instruction for use.

The same applies for medical devices used intraorally that the safety is ensured by following in the instructions for use.

TPO will most likely soon be classified as Repr. 1B (harmonised classification). The medical devices described in this article, which are manufactured from resin mixtures containing TPO, can be deemed as safe provided there is correct curing during fabrication. Curing minimises the TPO content in the medical device, as the TPO is consumed during the curing process as shown inTable 3. For uncured products the determined MOS is <1 and therefore an adverse effect on health cannot be excluded. This can be prevented, however, if the product is cured correctly and with an MOS >1. An MOS value greater than 1 usually implys nonegative effects on human health.

- It should be mentioned that the uncured products described in this article represent a worst-case situation, namely that of the resin mixture (liquid raw material).
- The authors wish to emphasize that the conclusions presented in this article are only valid for the products presented and are not generally applicable for other resin mixtures or products. According to the MDR (Annex I GSPR 10.4) every manufacturer has the obligation to conduct a benefit-risk assessment.

Annex A: Side reactions

Conceivable side reactions are shown in Figure 6.

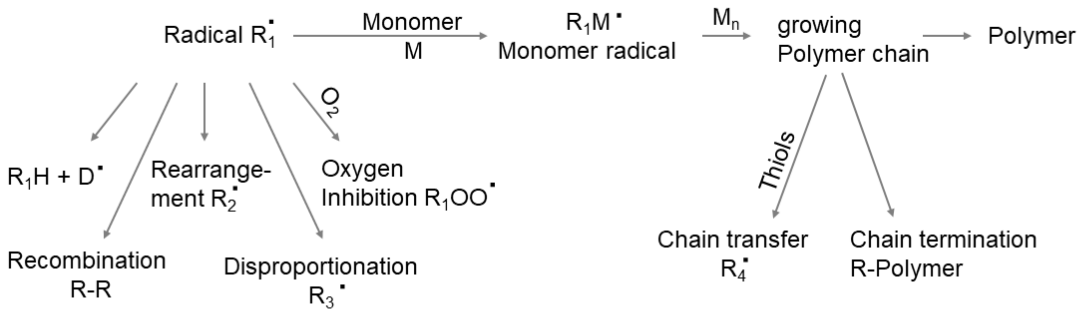


Fig. 6. Possible side reactions following radical formation. [1]

Recombination reactions are the simple reversion of the original fission reaction, which results in the initial PI.

Rearrangement reactions can in some cases lead to new, reactive radicals; others, in contrast, lead to deactivated neutral products.

Disproportionation reactions lead to two neutral species via the interaction of two identical radicals; again a deactivation reaction.

Oxygen inhibition is a reaction of any radical species with oxygen. This takes place on the surface or in the upper layers of the polymer during curing. The peroxy radicals created are relatively inert and do not contribute to polymerisation initiation. As a result oxygen can delay and inhibit polymerisation, which can lead to a sticky material surface.

Termination reactions are the addition of a radical to the growing terminal of a polymer chain. This results in a neutral species, which causes the end of the chain growth.

The majority of PIs will mainly form one or two of the reaction products cited; other photoproducts are usually only detectable in traces. [1]

The most likely side reaction of TPO is hydrogen abstraction of molecules in the surrounding area shown as an example in Figure 7.

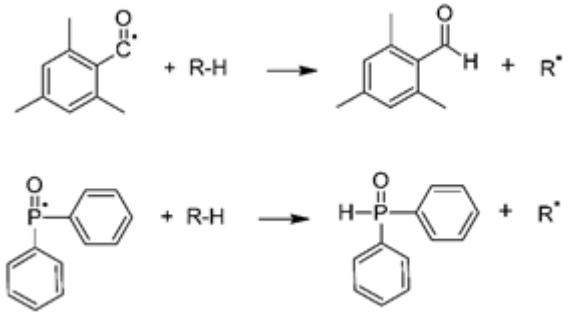


Fig. 7. Possible formation of by-products due to hydrogen abstraction.

The occurrence of recombination reactions of TPO is considered extremely unlikely due to its lower concentration. Relevant recombination products have been investigated in the literature but this was only possible using complex trapping agents. Moreover, the recombination reaction in these cases only reproduced the initial molecule, which was once again split.

Annex B: Selection factors for PI systems

The structure of a PI has basically been designed to produce radicals under UV light. In industrial and dental application the aim is for a process as efficient as possible; the majority of PIs available today therefore provide excellent curing properties. As already mentioned, some deactivating processes compete with this desired process, which can impede the photochemical reaction steps to radicals and formation of the polymer. The photoactivity of a mixture depends on a range of factors, e.g. the radiation dose, wavelength, absorption characteristic of the PI, the reactivity of the initiating radicals and the monomers or oligomers.

In the following the factors will be discussed, which should be considered when selecting a PI system. These represent chemical and physical phenomena that should be taken into account and balanced against one another to produce a reliable product. These phenomena are normally interlinked with one another and influence each other, which is visualised in Figure 8. This explains the background of each factor and highlights the interaction.

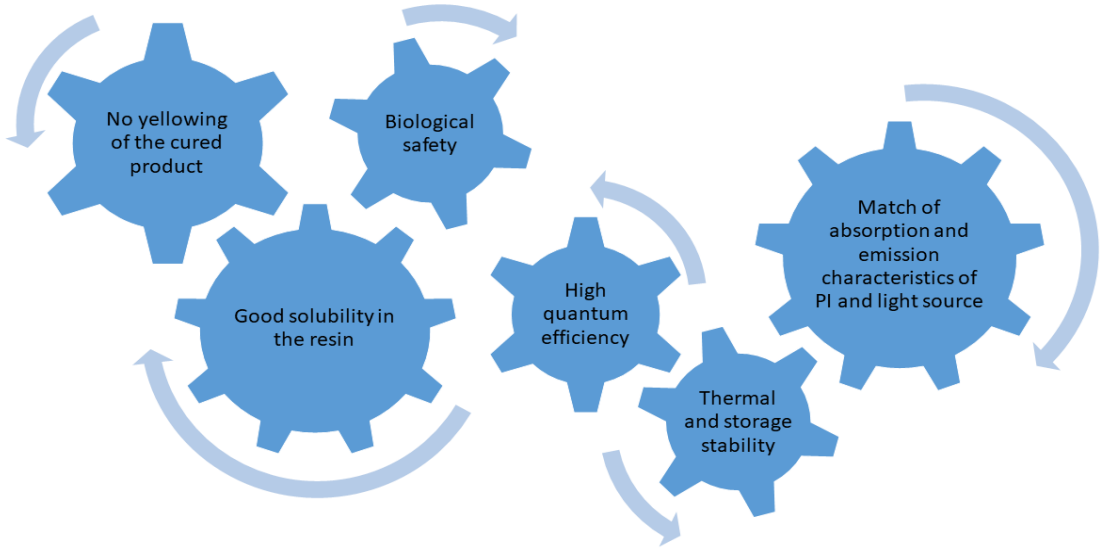


Fig. 8. The most important requirements of PIs.

Comparison of photoinitiator absorption and radiation source

The initiating step in the curing process is the absorption of UV energy by the PI. For efficient energy transfer from the light source to the PI adequate overlapping of their spectral regions (light emission and PI absorption) is required, because with this the energy absorbed by the PI is converted into chemically usable energy in the form of reactive radicals and polymerisation is started.

The spectrum of visible light begins in the longwave range with the colours red at 750 nm and then shifts from yellow over green to blue at 400 nm. The narrow band from 400 to 450 nm is called blue light or UV and can activate PIs with overlapping absorption. The UV range is associated with shorter wavelengths (100-400 nm), which is subdivided in UV-A (320-400 nm), UV-B (280-320 nm) and UV-C (200-280 nm). As the penetration power of UV and visible light depends on the wavelength, UV-C and UV-B are used for surface curing, while UV-A and visible light are essential for deep curing. Commercially available PIs for dental application can be activated by UV-A and blue light (315-450 nm), which is why these wavelengths are used.

A variety of light sources is available for light curing photocurable compositions, however only a few have been included in application in dental laboratories and practices. Another type of light source is a tungsten-halogen lamp (quartz-tungsten-halogen, QTH): this provides light in the wavelength of 370-550 nm with an intensity peak at approx. 465-470 nm, which matches well with the maximum absorption of camphorquinone. The irradiation of these lamps is between approx. 300-800 mW/cm². QTH lamps use electric current, which causes a tungsten filament in a halogen gas atmosphere to glow. A great deal of heat is generated, so that powerful, noisy coolers are necessary. Other limitations of this technology are short service life, long curing times and that operators must use filter glasses.

Argon-ion lasers (AIs) can be used as another type of light source for polymerisation of dental compositions. These are very effective due to the high, constant light intensity; curing is performed independently of the distance of the tip from the surface of the tooth, and the curing time is also reduced. On the other hand, there are also some disadvantages for this technology. These include a high price, relatively high waste heat, the size of the unit and the necessity of having to be used by the treating dentist and not by the dental technician or assistants.

Plasma arc lamps can also be used. The core unit consists of two tungsten electrodes, which are mounted at a specific distance in a high-pressure argon chamber. The light is passed through a synthetic sapphire window via a parabolic mirror. The high potential between the electrodes produced by a voltage generates a spark, which ionises the gas and thus creating a conduction path through the gas. The irradiation of these types of lamps is normally approx. 2000 mW/cm² with a spectrum between 380 nm and 550 nm. Their main advantage is in the short polymerisation times; 3 s with one of these types of lamps corresponds to approx. 40-60 s with QTH lamps. However, investigations have shown that such a shortened polymerisation time is accompanied by increased shrinkage and microleakage. Other disadvantages of plasma arc lamps are the short service life, high costs and considerable heat generation, which is why they are used relatively rarely.

Today, LED lamps (light emitting diode) are mainly used for light curing. LEDs based on gallium nitride or other semiconductor systems can emit blue light. Modern LED systems have a range of advantages compared with the technologies previously mentioned: their irradiation is very high with 1000-3000 mW/cm², and they are mostly light, compact, cost-effective, energy saving and generate barely any waste heat. These decisive advantages have in the meantime resulted in their widespread use. LEDs are now the most reliable and therefore preferred light source for the majority of users in dentistry. [2]

Photobleaching

PIs with an absorption maximum over 400 nm absorb the blue range of the visible spectrum and therefore appear yellow. Although phosphine oxides have this intrinsic colour, they lose it by so-called photobleaching due to exposure to UV or visible light.

This effect has two advantages: firstly, with UV curing the exposed layer is more permeable to light, which is why deeper layers are reached and thus curing is also initiated in this area. Secondly, the bleaching effect ensures that ideally an end product can be obtained that is not discoloured.

The phosphine oxides TPO, TPO-L and BAPO have a pronounced absorption of approx. 395 nm and enable high depth curing, which among other things can be attributed to the photobleaching mentioned. There are only few other Type 1 initiator systems that are able to produce high depth curing with LED arrays at 395 nm. Furthermore, there is the higher quantum yield (number of radicals produced per irradiated photons) for TPO, followed by BAPO and CQ. Although the mechanism for radical production is different for each PI system, in principle the production of two radicals per absorbed photon is to be expected. [3]

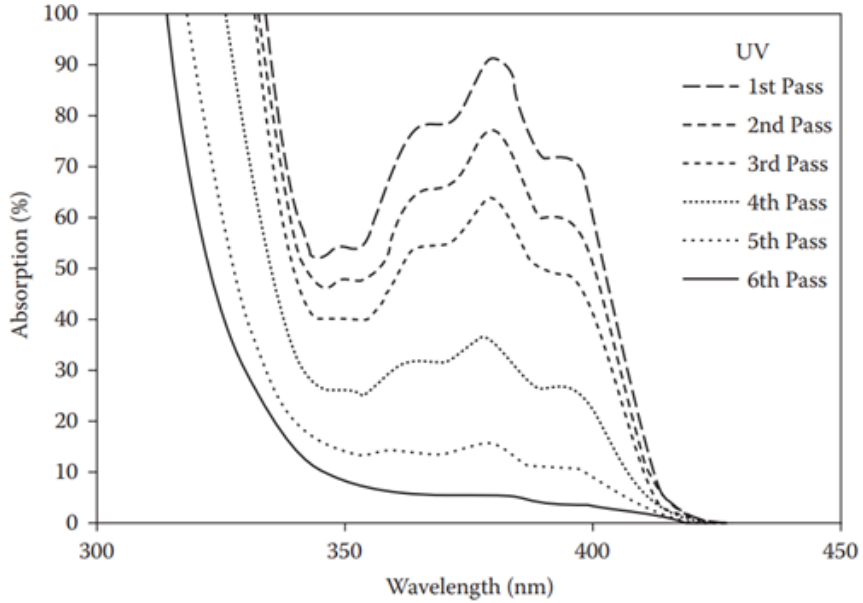


Fig. 9. Photobleaching of the phosphine oxide TPO with resulting excellent depth curing and colourless layers [1].

In contrast to phosphine oxides, camphorquinone does not possess any photobleaching properties, which is why curing of high layer thicknesses is problematic. Furthermore, the ageing and yellowing processes of the amines of the CQ/amine system used as synergists are inferior, which is contrary to aesthetic requirements.

Absorption by particulate components

Inorganic fillers are often used in dental compositions. These can be, for example oxides (silicates, aluminium-, titanium- and zirconium- oxides), base silicate glass (barium/strontium glass) or biomimetic materials such as hydroxylapatite ($(Ca_5(PO_4)_3OH$). By selecting suitable fillers important mechanical properties such as abrasion resistance and breaking strength can be improved or shrinkage reduced. For shade reproduction of the product different, generally inorganic pigments are used. The two particulate components cited can absorb light energy or scatter the light, which competes with light absorption by the PI (Figure 10). The entire system must therefore be optimised by selection of the raw material and adaptation of its concentrations to ensure the necessary curing.

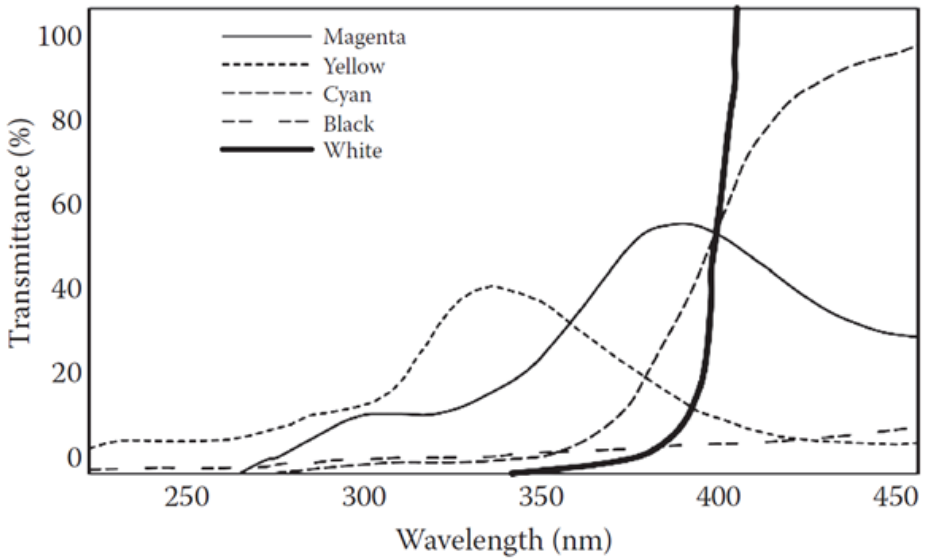


Fig. 10. Transmission spectra of pigments. [1]

Efficient polymerisation can be achieved by optimally coordinating transmission of the pigments, absorption of the PI system and emission spectrum of the light source. The PI system must therefore be selected, so that it absorbs from UV-A range to the visible range. The phosphine oxides TPO, TPO-L and BAPO partially absorb over 420 nm, whereby they provide the ideal requirements for dental applications. Their higher quantum yield and suitable absorption spectrum together with their photobleaching properties often make them the preferred choice compared to CQ/amine combinations.

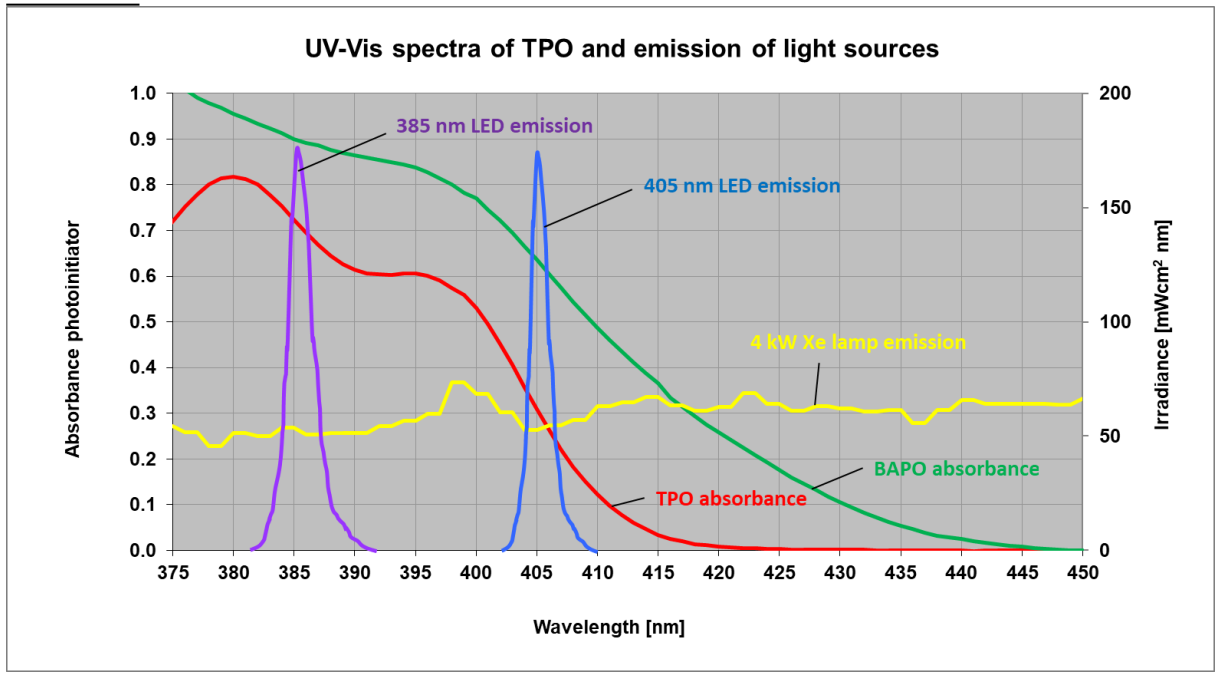


Fig. 11. Absorption spectra of TPO and BAPO and emission spectra of commercially available light sources.

Quantum yield

The quantum yield sets the ratio of the number of photons necessary to initiate a further process such as fluorescence or a chemical reaction (here: radical generation). A low quantum yield can have a negative impact on the reaction speed and a lower degree of polymerisation, which can favour the extractability of harmful components. Taking into account the competitive absorption and light scatterer mentioned, a high quantum yield of the PI is therefore important to utilise the available light energy efficiently for radical generation. A high quantum yield also enables a reduction of the PI concentration required in the photocurable composition.

Annex C: Camphorquinone/tertiary amines

One of the frequently encountered PI systems for dental systems consists of D, L-camphorquinone (CQ) and a tertiary amine. [4] The CQ combined with a variety of synergists absorbs in the entire blue range of the visible spectrum (400-500 nm), which enables the use of lower energy radiation and compared with older systems is considerably more gentle on living tissue.

Radical formation of Type-2 PI starts with photosensitisation of CQ, which abstracts a hydrogen atom in the excited state of amine synergists (Figure 12).

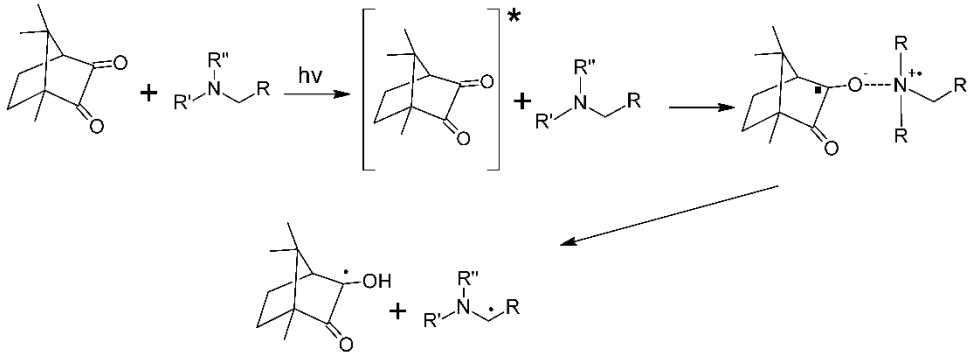


Fig. 12. Mechanism of the radical formation of CQ/amine systems. [5]

It is generally accepted tertiary amines function as reducing agents or hydrogen donors. If the polymerisation power of CQ with CQ/amine systems is compared, it is clear that the CQ/amine system is more effective than CQ alone. [6, 7] From a technical point of view there is a high number of amines available as synergists, however, the requirements for biocompatibility and with regard to aesthetics limits the selection. Amine ethyl 4-(dimethylamino)benzoate (EDMAB) is often used in combination with CQ in dental formulations as an effective hydrogen donor. Short curing times with relatively low concentrations can be achieved using this amine. [7] Another frequently used amine is 2-(dimethylamino)ethyl methacrylate (DMAEMA), which is incorporated in the polymer via the methacrylate group. Technical literature provides information that the use of DMAEMA results in lower polymerisation speeds and conversions in comparison with aromatic amines. [8, 9] The low reactivity of DMAEMA is attributed to the fact that DMAEMA tends to have a deactivation reaction with oxygen. DMAEMA also carries a methacrylate group, which in the presence of radicals encourages this molecule to form dimers or oligomers with itself. [9]

CQ and CQ/amine systems also have other disadvantages. One of these is the yellow colour of the end product, as CQ absorbs at 470 nm, the reflected shade is therefore between yellow and orange. Camphorquinone does not change its structure during radical formation and consequently

retains its colour. However, it is not only CQ that is responsible for the final shade but also the proportion of tertiary amines, which cause considerable discoloration over time. The photobleaching properties of this system are insignificant. The use of CQ/amine is limited due to these disadvantages. [10]

One disadvantage of this system is the necessity for two components, which must come close together spatially for the radical formation process. A high viscosity of the mixture has a negative effect, as the reaction is diffusion controlled. [10]

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