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DMFR 50TH ANNIVERSARY: REVIEW ARTICLE

Radiobiological risks following dentomaxillofacial imaging: should we be concerned?

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Objectives: This review aimed to present studies that prospectively investigated biological effects in patients following diagnostic dentomaxillofacial radiology (DMFR).
Methods: Literature was systematically searched to retrieve all studies assessing radiobiological effects of using X-ray imaging in the dentomaxillofacial area, with reference to radiobiological outcomes for other imaging modalities and fields.
Results: There is a lot of variability in the reported radiobiological assessment methods and radiation dose measures, making comparisons of radiobiological studies challenging. Most radiological DMFR studies are focusing on genotoxicity and cytotoxicity, data for 2D dentomaxillofacial radiographs, albeit with some methodological weakness biasing the results. For CBCT, available evidence is limited and few studies include comparative data on both adults and children.
Conclusions In the future, one will have to strive towards patient-specific measures by considering age, gender and other individual radiation sensitivity-related factors. Ultimately, future radioprotection strategies should build further on the concept of personalized medicine, with patient-specific optimization of the imaging protocol, based on radiobiological variables.
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Introduction

Ionizing radiation (IR) is ubiquitous in the environment and can be naturally occurring as well as man-made. It is well known that exposure to high doses of IR effect can cause health effects including tissue reactions, previously termed 'deterministic effects', and stochastic effects. Tissue reactions were observed almost immediately after the discovery of X-rays.[1–3] They are associated with high doses of IR and occur over a short period of time (*i.e.* within hours up to a few weeks). For tissue reactions, a threshold dose exists, below which no IR effect has been detected.[4] At low doses, which are defined as being lower than 100 milligrays (mGy), mostly stochastic effects occur. These stochastic effects

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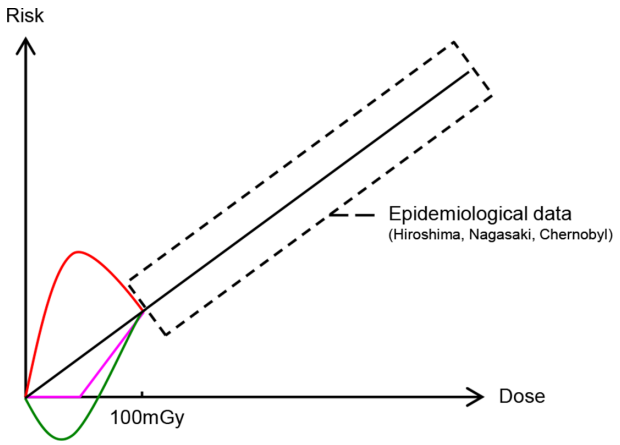

Figure 1 Graphical representation of the different models explaining the dose–response relationship in the low dose range. Four models are represented that show potential dose–response relationships for radiation exposure below 100 milliGray. The linear-no-threshold model (black line), the linear-threshold model (pink line), the hormetic model (green line) and the hypersensitivity model (red line). As depicted by the linear part of the curve, the effects associated with doses higher than 100 milliGray are well understood. Thanks to epidemiological data that are available from the Hiroshima and Nagasaki bombings, as well as the Chernobyl disaster.

(*e.g.* carcinogenesis) are observed over a longer period of time (*i.e.* months up to several years). For low doses, the uncertainty of the stochastic effects (*e.g.* radiation-induced cancer and hereditary disorders) increases.[5] This increase is caused by a lack of statistical significance of the epidemiological data. Most of these data come from Japanese atomic bomb survivors, medically and occupationally exposed populations as well as environmentally exposed groups.[6] For exposure to low doses, policymakers use models based on these epidemiological data.

Currently, the linear non-threshold (LNT) model is used to estimate stochastic effects involved in the low dose range. The LNT model assumes that there is no threshold dose below which no additional health risk occurs and that the risk increases linearly with the absorbed dose.[7] However, it is not the only model for exposure to low doses of IR (Figure 1).[8–11] Besides the LNT model, a threshold model exists, that suggests that the IR dose must exceed a certain threshold dose in order to initiate a biological response. Per definition, no effects are expected to occur when exposed to doses below the threshold dose. A third model, the hormetic model, suggests that low doses of IR could induce beneficial effects, resulting in a reduced risk.[8] Finally, the hypersensitivity model assumes that due to hypersensitivity of cells to very low doses, the biological risks may be greater when exposed to low doses of IR.[12] Thus far, evidence definitely proving or disproving these models is lacking. Although, epidemiological data support the LNT model for doses higher than 100 mGy, there is no clear consensus about which model to use in the low dose range due to a lack of supporting data.[9–11,13,14]

Besides the models described in the previous paragraph, other biological phenomena could occur. One such phenomenon is the presumption that organisms can 'adapt' to IR exposure. This is called an adaptive response.[15] Low doses are thought to elicit a biological response, which results in the activation of several genes/proteins that help the organism's defence against a similar insult in the future. For example, after exposure to low doses of IR, detoxification of free radicals and the DNA repair systems could improve, as well as the antioxidant production and cell cycle regulation. All these processes will improve the organism's defence against future IR exposure, thereby increasing its radioresistance.[15,16]

In order to accurately estimate radiation-induced health risks, it is important to know how much energy or which dose is absorbed by the human body and its organs. Furthermore, it is important to know the dose–effect relationship. Different units are used in the international system of units (SI) to express radiation doses: the absorbed dose, the equivalent dose and the effective dose. Additionally, in medical diagnostics the dose–length product (DLP) is frequently used as well (Table 1).

Knowledge about low dose radiation induced health risks is particularly important in the field of diagnostic imaging using IR, in which typically doses much lower than 100 mGy are used. The amount of medical examinations using IR (*e.g.* computed tomography scan, nuclear medicine, X-ray radiography …) has increased by a sixfold globally in the per capita medical radiation exposure over the previous 25–30 years.[21] This increase in examinations coincides with an increase in the global average annual effective dose per caput from medical IR exposure, which increased from 0.35 millisieverts (mSv) per caput in 1988 to 0.62 mSv per caput in 2008, an increase of 77%.[22] Therefore, medical exposure to IR accounts for about 14% of the total annual exposure worldwide, which makes it the largest man-made source of IR exposure to the general population.[22,23]

The rapid increase in the use of IR for medical diagnostics and associated health concerns, have led to several retrospective epidemiological studies that investigated whether IR exposure due to medical diagnostics, such as CT scans, is associated with an increase in cancer incidence later in life. Pearce et al.[24] suggests that the use of CT scans in children could triple the risk of leukemia and brain cancers later in life.[24] Additionally, a large Australian cohort study found an increase in cancer incidence that was 24% greater in children exposed to CT scans than in unexposed children.[25] Despite the potential links between diagnostic radiology and radiation-induced malignancies, absolute evidence from prospective studies is lacking.[10,26] This may also be true for dentomaxillofacial two-dimensional (2D) and three-dimensional (3D) imaging, which has been receiving far less attention in the current literature and of which reports have focused typically on stochastic models.[27,28]

Table 1 Overview of different radiation dose units.[17]

Radiation dose	*Unit*	*Symbol*	*Calculation*	*What does it mean?*
Absorbed dose	Gray (Gy) (J•kg^{-1})	D	$D = \frac{\varepsilon}{m_T}$	Represents the amount of radiation energy that is absorbed per unit of mass of a substance.[17,18] (
Equivalent dose	Sievert (Sv) (J•kg^{-1})	HT	$HT = \sum_R \varpi_R D_{T,R}$	Takes into account the type of radiation as well as its effectiveness. When exposed to multiple radiation types, the equivalent doses of each radiation type must be calculated and then summated.[18,19]
Effective dose	Sievert (Sv) (J•kg^{-1})	E	$E = \sum_T \varpi_T H_T + \varpi_{rem} H_{rem}$	Takes into account the equivalent doses in all specified tissues and organs of the body, which is multiplied by a tissue-specific weighting factor. Represents the health risk, i.e. the probability of cancer induction and/or genetic effects.[19]
Dose-length product	DLP	Gy•cm	CTDIvol ((1/3) x radiationcenter + (2/3) x radiationperiphery)/pitch)x scan length	Used to calculate the total absorbed dose of radiation a patient is exposed to in a computed tomography examination and is therefore directly related to the stochastic risk.[20] Note: DLP is not equal to the effective dose.
Dose area product	DAP	Gy·cm²	D x Scan area	Dose Area Product (DAP) is a measure of the total amount of radiation delivered to a person, with the area of the irradiated tissue taken into account.

$\bar{\varepsilon}$, mean energy; D_(T,R), D in a target tissue (T) due to radiation type 'R'; ω_R, radiation weighting factor; ω_T, tissue weighting factor; m_T, mass of volume of interest; rem, remainder tissues.

Indeed, up to a 20-fold change in effective dose has been observed for different cone beam CT (CBCT) devices indicating a need for clinical recommendations as well as optimization of CBCT-based machine-dependent, patient-specific and indication-oriented variables.[29,30] In this regard, age-dependent radiation sensitivity should be taken into account, as children are more radiosensitive than adults.[31–33] This has led to concerns about potential radiation-induced health effects associated with diagnostic radiology, especially in the young population.[34–37]

The purpose of this review is to present studies that prospectively investigated biological effects in patients following dentomaxillofacial diagnostic imaging with X-rays. In particular, genotoxic and cytotoxic effects induced by plain radiography and CBCT as opposed to CT will be covered. A specific focus will placed on potential patient-specificity as well as gender- and age-related differences. Ultimately, we propose a reflection on how the current knowledge on biological effects can drive optimization strategies, mainly in children and adolescents in need of dentomaxillofacial imaging.

Assessing biological effects following low dose ionizing radiation exposure

Assessing the biological effects of (low dose) IR exposure is usually done via cytotoxicity and genotoxicity assays. Cytotoxicity means that IR exposure can be toxic to the cell, which usually leads to cell death or necrosis. This can be seen microscopically by observing nuclear changes. These changes include karyolysis (dissolution of chromatin), pyknosis (chromatin condensation) and karyorrhexis (fragmentation of pyknotic nuclei). If genotoxicity is detected, this indicates a potential risk of developing malignancies later in life. Genotoxicity markers that are mostly analyzed are chromosome aberration frequency (*i.e.* dicentric chromosomes, ring chromosomes), micronuclei (MN) frequency, single cell gel

electrophoresis assay (also known as comet assay), and histone H2AX phosphorylated on serine 139 (γH2AX) foci.

Dicentric chromosome frequencies in peripheral blood lymphocytes have been the golden standard to estimate recent IR exposure in radiation emergency medicine.[38,39] The half-life of dicentric chromosomes is between 6 and 12 months. Similar to dicentric chromosomes, ring chromosomes are known to increase in a dose-dependent manner, from low to high doses[39,40]

The MN assay is the most frequently used assay for genotoxicity of chemicals/pharmaceuticals.[41] A MN is formed during the anaphase of mitosis or meiosis and are cytoplasmic bodies having a portion of an acentric chromosome or a whole chromosome that was not carried to the opposite poles during the anaphase. Their formation results in a daughter cell lacking a (part of a) chromosome.[42] The MN assay has been successfully used as a biomonitoring tool, *e.g.* in industrial radiographers and hospital workers exposed to low doses of IR.[43–45]

The comet assay is a sensitive technique for the detection of DNA damage at the level of the individual eukaryotic cells. It is used as a standard technique for evaluation of DNA damage/repair, biomonitoring and genotoxicity testing. The results from the comet assay are a measure for the amount of DNA double strand breaks (DSBs) present within each cell.[46] The comet assay has been used for many years to detect DNA damage induced by IR. For example, in nuclear medicine personnel and other hospital staff.[47,48] While the comet assay is mostly sensitivity to large amounts of DNA damage, it can also be used to detect the effects of diagnostic X-rays in Children and in stem cells.[49,50]

Finally, γH2AX is part of the DNA damage response, a signaling cascade that results in the recruitment of multiple proteins to the vicinity of DNA DSBs. γH2AX forms DNA damage foci and show a quantitative relationship between the number of foci and the number of DSBs.[51–53] The γH2AX assay has been used frequently to assess IR-induced DNA damage. Because of its sensitivity to low doses of ionizing radiation, it has been used in wide variety of studies: health workers, patients exposed to radionuclides, low dose biodosimetry purposes and even for *in vitro* and *in vivo* CBCT simulations.[54–60] Results from these assays will be discussed (if data are available) for CT scans, CBCT scans, and plain radiographs. Attention will be given to dentomaxillofacial imaging applications. In this literature review performed between January 2019 and March 2021, Web of Science was searched using the following key words: computed tomography, radiology, cone beam computed tomography, biological effects, health effects. These were filtered to only include publications who followed-up patients from the medical examination up to the point of testing (prospective studies). Epidemiological and/or retrospective studies were excluded from this literature review.

Radiobiologic effect in relation to computed tomography

Since its introduction in the 1970s, the use of CT scans has increased rapidly. For example, in 2008 (Belgium), 180 examinations were performed per 1000 capita, whereas in 2017, this increased to 200 per 1000 capita.[61] In 2017, the use of CT scans in Organisation for Economic Cooperation and Development (OECD) countries ranged from 37 per 1000 capita (Finland) to 231 per 1000 capita (Japan).[62] CT scans are mostly used to diagnose muscle and bone disorders, detect internal bleeding, localize a tumor, as a guide during surgery or radiotherapy and to monitor disease/treatment progression. Depending on various settings, the organ doses received per CT scans is about 15 mSv in adults, whereas it can be up to 30 mSv in neonates. Since multiple scans are often required to follow-up the patient, the accumulated dose can increase rapidly.[63]

Several studies reported significant increases in the number of dicentric chromosomes in peripheral blood lymphocytes (PBLs) after CT scans in adult patients.[64–66] In children younger than 15 years old, similar results were also observed.[32,67] Abe et al[65] did not find a correlation between the number of dicentric chromosomes and the effective dose.[65] Furthermore, these studies suggest that younger children (<10 years old) in particular have increased radiosensitivity, especially at higher absorbed doses (mean dose of 12.9 mGy).[67]

In adults, significant increases in the number of ring chromosomes in PBLs were observed 15 min after a CT scan.[64,68] To the best of our knowledge, no such studies in children were published so far.

Significant increases in the MN frequency were observed in PBLs from adults a few hours after CT exposure.[66] In another study, Khattab et al[69] showed that the number of MN does not increase significantly in infants that undergo CT followed by cardiac catheterization.[69] However, this was only the case if the infant was never exposed to CT scans before. Interestingly, in infants exposed to previous CT scan(s), MN frequencies measured after a scheduled CT scan were significantly higher than before that CT scan. These results suggest that prior CT scans increase the cellular responses to subsequent CT exposures.[69]

Multiple studies in adults show that there are significant increases in the number of γH2AX foci in PBLs several minutes/hours after CT scans.[70–85] An important observation is that exposure to multiple CT scans causes more DSBs as compared to single scan.[85] In children, similar effects were observed.[86,87] It is noteworthy that there are 15 studies reporting increases in γH2AX foci after CT scans in adults, whereas so far only two studies investigated this in children. Also worth mentioning is that several of these studies found that the use of a contrast medium (CM), which is frequently used in CT examinations, can increase the amount of radiation-induced γH2AX foci.[72,76,81,84] Furthermore, Wang et al[84] suggest that the use of a contrast agent itself can induce γH2AX foci.[84]

Table 2 Overview of the biological effects detected in patients following cone beam CT

Assay	*Gender*	*Age (years)*	*Dose*	*Time of sampling*	*Tissue examined*	*Tissue used*	*Biological effects*	*References*
MN assay	9 females 10 males	26.8 ± 5.0	Not mentioned	Before and 10 days after cone beam computed tomography	Oral cavity	Exfoliated oral mucosa cells	No induction of MN, but induction cytotoxicity (pyknosis, karyolysis, karyorrhexis)	Carlin *et al.* (2010)[101]
	10 girls 14 boys	11 ± 1.2	Range: 287 μSv - 304 μSv					Lorenzoni *et al.* (2013)[102]
	39 females seven males	23–42	Range: 448.15–730.79 mGy·cm^2					Yang *et al.* (2017)[103]
	17 females 12 males	45.8 ± 12.5	Not mentioned				Significant induction of MN, and cytotoxicity (pyknosis, karyolysis, karyorrhexis)	Da Fonte *et al.* (2018)[104]
	70 females 28 males	23.63 ± 6.64	Range: 0.18 mGy – 3.54 mGy				Significant induction of MN, and cytotoxicity (pyknosis, karyolysis, karyorrhexis) above 1 mGy. Below 1 mGy, only significant induction of karyorrhexis.	Li *et al.* (2018)[105]

MN, micronucleus.

Dentomaxillofacial cone beam computed tomography

CBCT is a relatively new and innovative diagnostic imaging technique introduced in oral health care at the turn of the century.[88,89] Global numbers of the use of CBCT are not commonly available but a recent Belgian survey found that 20% of the Belgian dentists have access to a CBCT device, which is a remarkable increase compared to a decade before.[90] It is noteworthy that only 9% of the general dental practitioners and 12% of the orthodontists had access, while more than 60% of the oral and maxillofacial surgeons and periodontologists had access.[90] As with CT and X-ray radiography scans, a wide range of CBCT doses is used in the clinic, typically ranging from about 0.01–1.100 mSv per examination.[36,91–96] CBCT doses are lower than CT doses, yet, they are higher than classical 2D dental radiography techniques.[29,97,98] Though, as with CT and radiography, multiple scans might be required, which causes a rapid increase in the cumulative dose. More recently, the IR dose to pediatric patients has become a major concern among clinicians.[92,99] In 2010, the New York Times brought this to the attention of the general public with the publication of the article entitled "Radiation Worries for Children in Dentists' Chairs".[100] An overview of studies reporting on CBCT-related biological effects in patients are summarized in Table 2.

There is evidence that CBCT examinations can cause a significant increase in MN frequency in adults.[104–106] Contrary, there are studies that suggest that the MN frequency does not change in adults.[101,103] So far, only one study investigated the biological effects of CBCT in children. In this study, no increase in MN frequency was observed following CBCT examination.[102] However, as with CT and radiography, most studies found a significant increase in cytotoxicity markers both in adults and children.[101–105] To our knowledge, only one *in vitro60* and no clinical studies exist that report on DNA DSB induction following CBCT. In this study, no DNA DSBs were found to be induced in buccal mucosal cells from either children or adults after a single CBCT examination.

Plain dentomaxillofacial radiography

X-ray radiographs have been used in medicine since the discovery of X-rays over 120 years ago. Ever since, radiographs have been widely used in medical diagnostics and the effective dose ranges from 0.001 to 0.1 mSv.[84] Also, radiography is mostly used for bone examinations, dental examinations, mammography and orthopedic evaluations. In dentomaxillofacial radiography, plain radiographs refer mostly to panoramic, cephalometric and intraoral radiographs.[107] These techniques give a 2D view of the maxilla, mandible, teeth, temporomandibular joints and maxillary sinuses. Yet, these anatomical structures have complex 3D organizations. In consequence, as in other fields, dentomaxillofacial imaging has moved towards 3D imaging in cases were the clinical use is justified.[108] Considering 3D images, CBCT has greatly reduced the absorbed dose compared to traditional CT.[94] However, CBCT produces a greater X-ray dose than a panoramic radiograph.[109] Furthermore, it is also becoming more preoccupant that there is a wide span of delivered effective doses to the patient for different CBCT devices.[110,111] Nevertheless, as with CT scans, multiple radiographs are often required, resulting in a higher cumulative dose. Studies reporting on plain radiography-related biological effects in patients are summarized in Table 3.

It has been known since the first half of the 20th century that exposure to X-ray radiographs causes chromosome aberrations.[134] Since then, most studies that focus on biological effects following radiography,

Table 3 Overview of the biological effects detected in patients following X-ray radiography

Assay	*Gender*	*Age (years)*	*Dose*	*Time of sampling*	*Tissue examined*	*Tissue used*	*Biological effects*	*References*
	24 females7 males	24 ± 1.023	21.4 μSv	Before and 10 days after examination	Oral cavity	Exfoliated oral mucosa cells	No induction of MN, and cytotoxicity (pyknosis, karyolysis). Significant induction of karyorrhexis.	Cerqueira *et al.* (2004)[112]
	31 females9 males	20 subjects ≤ 22.520 subjects > 22.5	21.4 μSv			keratinized mucosa of theupper dental arch	Significant induction of MN	Cerqueira *et al.* (2008) [113]
	nine girls8 boys	7.70 ± 1.50	0.08 Roentgen(Entrance dose)			Exfoliated oral mucosa cells	No induction of MN, and cytotoxicity (pyknosis, karyolysis). Significant induction of karyorrhexis.	Angelieri *et al.* (2007)[114]
	42 males	18–40	0.057 mSv(Average dose)			Cells of the lateral border of the tongue	No induction of MN, but increased cytotoxicity (pyknosis, karyolysis, karyorrhexis). The number of karyorrhexis and binucleated cells was greater after multiple X-rays	Da Silva *et al.* (2007)[115]
	20 females12 males	24–73	Not mentioned	Before and 10 ± 2 days after examination		Exfoliated oral mucosa cells	No induction of MN, but increased cytotoxicity (pyknosis, karyolysis, karyorrhexis).	Popova *et al.* (2007)[116]
	31 females9 males	26 ± 9.18	21.4 μSv	Before and 10 days after examination		Keratinized gingival cells	Significant induction of MN, and cytotoxicity (pyknosis, karyolysis, karyorrhexis)	Cerqueira *et al.* (2008)[113]
	28 females11 males	39.6 ± 13	0.08 Roentgen(Entrance dose)			Exfoliated oral mucosa cells	No induction of MN, but increased cytotoxicity (pyknosis, karyolysis, karyorrhexis)	Ribeiro and Angelieri (2008)[117]
	six females11 males9 girls8 boys	39.6 ± 5.47.7±1.5	0.08 Roentgen(Entrance dose)				Both in adults and children, no induction of MN, but increased cytotoxicity (pyknosis, karyolysis, karyorrhexis)	Ribeiro *et al.* (2008)[118]
	12 females20 males	Mean: 38.65	0.08 Roentgen(Entrance dose)				No induction of MN, but increased cytotoxicity (pyknosis, karyolysis, karyorrhexis)	Angelieri *et al.* (2010a)[119]
	12 females6 males	14.2 ± 1.4	Not mentioned					Angelieri *et al.* (2010b)[120]
	20 patients(gender not specified)	Children(Age not specified)	Not available	Not mentioned				El-Ashiry *et al.* (2010)[121]
	13 girls7 boys	Apr-14	Range: 0.13–0.29(entrance dose)	Before and 30 min after examination	Chest	Peripheral blood lymphocytes	Significant induction of MN	Gajski *et al.* (2011)[122]
	15 females15 males	20–23	0.046 Roentgen(Entrance dose)	Before and 10 days after examination	Oral cavity	Exfoliated oral mucosa cells	No induction of MN, but increased cytotoxicity (pyknosis, karyolysis, karyorrhexis)	Ribeiro *et al.* (2011)[123]
	10 females15 males	11.2 ± 1.4	Not available					Lorenzoni *et al.* (2012)[124]
	80 patients	Adults(age not specified)	Not available				No induction of MN in buccal cells.Significant induction of MN in gingival epithelial cells.	Sheikh *et al.* (2012)[125]
Micronucleus assay								
	90 patients	Adults(age not specified)	Not available				No induction of MN, but increased cytotoxicity (pyknosis, karyolysis, karyorrhexis)	Thomas *et al.* (2012)[126]
	41 females19 males	27.63 ± 10.93	0.325 mGy/sec(no exact dose mentioned)				Significant induction of MN	Waingade and Medikeri (2012)[127]

(Continued)

Table 3 (Continued)

Assay	*Gender*	*Age (years)*	*Dose*	*Time of sampling*	*Tissue examined*	*Tissue used*	*Biological effects*	*References*
	32 females21 males	25.21 ± 12.67	0.325 mGy/sec(no exact dose mentioned)			Exfoliated oral mucosa cells and keratinized gingiva cells	Significant induction of MN in oral mucosa cells and a significant correlation was observed between the age of the subjects and number of MN	Arora *et al.* (2014)[128]
	20 patients(gender not specified)	Children(age not specified)	21.4 mSv(average dose)			Exfoliated oral mucosa cells	No induction of MN, but increased cytotoxicity (pyknosis, karyolysis, karyorrhexis)	Agarwal *et al.* (2015)[129]
	20 girls20 boys	07-Dec	Not mentioned	Before and 10 ± 2 days after examination			Significant induction of MN	Preethi *et al.* (2016)[130]
	70 females	23.63 ± 6.64	Range:	Before and 10 days after			Significant induction of MN, and cytotoxicity	Li *et al.* (2018)[102]
	28 males		0.18 mGy – 3.54 mGy	examination			(pyknosis, karyolysis, karyorrhexis) above 1 mGy. Below 1 mGy, only significant induction of karyorrhexis.	
Comet	14 girls6 boys	May-14	Range: 0–0.29	Before and 30 min after examination	Chest	Peripheral blood lymphocytes	Significant increase of DNA damage following radiography.	Milkovic *et al.* (2009)[50]
	20 patients(gender not specified)	Adults(age not specified)	Not available	Before and 30 min or 24 h after examination	Oral cavity	Exfoliated oral mucosa cells	Significant increase of DNA damage 30 min following radiography, but not after 24 h	Yanuaryska *et al.* (2018)[131]
γH2AX	45 females55 males	20–77	23.4 mGy(average dose)	Before and 20 min after examination	Oral cavity	Exfoliated oral mucosa cells	Increased number of γH2AX foci.	Yoon *et al.* (2009)[132]
	20 females	39–71	Range: 7.1–41.1	Before and 5 min after examination	Breasts	Systemic blood lymphocytes		Schwab *et al.* (2013)[133]

MN, micronucleus.

rely on the MN assay. Although many studies report no statistical differences in MN frequency following radiography examinations in adults,[115–120,123,125,126] significant increases in cytotoxicity markers (*i.e.* pyknosis, karyolysis, and karyorrhexis) are observed. Other studies report significant increases in MN frequency as well as cytotoxicity markers following dental radiography examinations.[105,113,125,127,128] Contrary, Cerqueira *et al* found no changes in MN frequency and cytotoxicity markers in adults, except for karyorrhexis in exfoliated cells from oral mucosa..[112] However, on keratinized mucosa cells Cerqueira et al.[113] found changes in MN frequency and cytotoxicity marker.[113] In children, an increase in MN frequency following dental radiography was reported.[122,130] However, as with adults, there are also studies that only report an increase in cytotoxicity.[102,114,118,121,124,129,135] Ribeiro *et al* compared the MN frequency and cytotoxicity markers between adults and children following dental radiography. They found no evidence that children are more radiosensitive than adults.[118] On the other hand, there are reports showing that there is a significant correlation between the age of subjects (mean age: 25.21 ± 12.67) and micronucleus count, contradicting previous results from Ribeiro *et al*.[125,128] Note that these studies found this age correlation in an adult patient group and that these results might not be extrapolated to children.

Comet assay data suggest that a radiography scan results in a significant increase in DNA DSBs in adults.[131] Similar data were obtained from children.[50] To our knowledge, these are the only two studies that reported on this and therefore should be interpreted with caution, given the many observed contradictions from the other assays that are described in this section.

Increases in the amount of γH2AX after radiography in adults was reported.[132,133,136] As with CT scans, it was shown for radiographs (*i.e.* mammography in this study) that there is a low-dose effect, and a low and repeated dose effect.[136] To our knowledge, no studies reported changes in γH2AX foci in children following radiography. Therefore no information is available on age-related differences (children *vs* adults).

Ongoing challenges

Health risks associated with exposure to high doses of IR (>100 mGy) are currently well-known thanks to epidemiological studies. While risks associated with exposure to low doses of IR, such as those used in medical diagnostics, have been suggested through retrospective epidemiological studies, controversy about low dose effects still exists.[24,25] Furthermore, clear evidence from prospective studies is lacking.[26] Only a few of them

report a correlation between IR dose and the observed effect, which adds to both the controversy of the use of the LNT model for risk estimation and the low dose uncertainty. To further improve existing radioprotection guidelines, more biological data on health risks associated with exposure to low doses of IR are necessary.

Induction of DNA DSBs by several types of CT scans (*e.g.* whole body, thorax, abdomen, chest and head) has been clearly demonstrated in blood lymphocytes via the γH2AX assay: all studies found a significant increase in γH2AX foci following CT scans in lymphocytes. It was also shown that after 24 h, the amount of DNA DSBs returned to baseline levels. This indicates that although the DNA was severely damaged, the cells were still able to repair the DSBs. However, this does not mean that no mutations, such as base alterations, have occurred. Although data on dicentric chromosome and MN formation are available, these are less unanimous. It was shown that the frequency of dicentric chromosomes increases after CT scan, but data on MN are less clear. Kanagaraj et al[66] reported an increase in MN frequency only a few hours after CT examination, while Khattab et al[69] demonstrated that the MN frequency only increased if prior CT examinations were conducted in a patient. Only a few studies conducted MN assays, most likely due to the technical difficulty of chromosome analysis on a larger scale. It would be interesting to use more 'localized' samples, *e.g.* oral mucosa cells or even saliva samples in patients in which head and/or neck are examined. This is done for radiographs and CBCT patients, and could be very informative when applied in CT patients. It is clear that the (potential) adverse effects of CT examinations on human health have been subject of many studies, as is shown in this review. However, it is noteworthy that there is a lot of variation between these studies concerning doses used, patients included, and experimental set-up.

It has been shown that X-ray examinations, like CT scans, can induce significant increases in DNA DSBs in patients. This was shown by the γH2AX (performed in two studies) and comet assays (performed in two studies). Both assays showed a significant increase in DNA DSBs shortly after a radiograph was taken. Unlike the data from CT scans where mostly yH2AX assays were performed, data from radiographs mainly rely on the MN assay (performed in 21 studies) to assess genotoxicity following exposure. Although all studies agree that radiographs cause an increase in cytotoxicity, mostly through increases in the frequency of karyorrhexis, there is a lot of disagreement on whether or not the MN frequency is also increased after radiography. While 10 studies report no increase in MN frequency, there are 6 studies that do report an increase after radiography. These data illustrate the controversy and difficulty of low dose research and also show why it is important to study the effects of low doses of IR thoroughly. Unlike the CT studies, mostly 'localized' tissues, such as oral epithelial cells, were used when assessing genotoxicity after radiography. Of the 26 studies included in this review, only 3 used blood samples for analysis. Therefore, it is less likely that the local effect of radiography was underestimated.

So far, only a small number of studies investigated potential biological effects associated with CBCT examinations, and the **majority** rely on the MN assay. This small number of studies is most likely due to the novelty of the device (it is about 20 years old). Nevertheless, since it is very frequently used in a pediatric population, data on age-related biological effects are necessary for radiation protection. As with CT and radiographs, data on genotoxicity are not unanimous. Two studies report an increase in MN frequency following CBCT examination, whereas three studies report no induction of MN. All five studies, however, report an increase in cytotoxicity. It is clear that these data are conflicting and that additional research is needed. Furthermore, all five studies used exfoliated oral mucosa cells to perform the MN assay, while other cell types (*e.g.* cell of the lateral border of the tongue or gingival cells) and/or biofluids (*e.g.* blood or saliva) may also be tissues worth investigating. Since there are a limited amount of data on γH2AX foci formation or the comet assay, no decisive conclusion can be made about induction of DNA DSBs following CBCT. One might expect an increase in DNA DSBs to occur, since it has been shown that radiographs induce DSBs and the IR doses used by CBCT devices are higher than those used in radiography. Monitoring γH2AX foci following CBCT examination in both adults and children is part of the scope of the European funded "Dentomaxillofacial paediatric imaging - an investigation towards low dose radiation induced risks" or DIMITRA study.[137] In this context, our recent study demonstrated the absence of an increased amount of DNA DSBs in buccal mucosal cells after CBCT examination (neither in children nor in adults).

Finally, a lot more studies were conducted in adults than in children. For CT, 23 studies were conducted in adults and only 5 studies included children. In one of the latter, the sample size was three, which results in a lack of statistical power on a population level.[87] Furthermore, data comparing adults and children in similar CT settings are lacking. Similarly, most studies on radiography were conducted on adults, whereas only four included children. As with CT scans and radiography, studies comparing genotoxicity in adults and children are lacking and those that are available contradict each other.[114,118,122,130] For CBCT, the number of studies including children is very low (*i.e.* one out of five). None of the above-mentioned studies followed the patients for longer than a few weeks. To better understand the extent of the observed genotoxicity following medical diagnostics, mostly in light of stochastic effects, long-term follow-up of patients is warranted.

Uncertainties on biological effects must drive optimization strategies

The sections above demonstrate how challenging it is to investigate the effects in dose levels compatible to dental and medical radiodiagnosis. The numerous variables that are combined in different manners, suffering effects of different sources, can generate controversial results and contestable conclusions. The epidemiological data on higher dose levels, however, seem to remain irreplaceable until now. In the meantime, scientists, radiobiologists and independent organizations are continuously investigating and reviewing the knowledge in order to propose up-to-date models on low-dose effects[138] Until proven the contrary, therefore, the LNT hypothesis remains the most reasonable track which means that justification and optimization principles must be strictly followed.

Justification and optimization, however, are challenging tasks in the daily practice. Despite many studies have proven the possibility to reduce considerably the dose keeping the imaging quality for diagnosis purposes and/or treatment plan, the translation of optimization, there is still room for improving the translation of optimization in clinical practice..[36] Others have been shown over indication of tridimensional exams in the dental field, failure on justification.[33,139–142] In addition, optimization becomes even more challenging when high-resolution 3D images (mostly higher-dose) are chosen for unjustifiable reasons. In this context, the ALADAIP principle (As Low As Diagnostically Acceptable being Indication-oriented and Patient-specific) comes into play,[96,143] proposing an exercise to ask what is the reason why the imaging exam is taken (indication) and who is the patient (age, sex, size and imaging exams history). It is well-known that X-ray diagnostic doses come from the most controllable source of IR, and despite its growing and the undeniable needs, it is fully manageable on exposure parameters and field of view.[144]

There is no doubt that a high level of uncertainty on low-dose effects remains. Moreover, despite the strong evidence regarding the higher radiation sensitivity of younger individuals, it has been even discussed if this this feature is applicable for low-dose. As already mentioned, however, studies demonstrated evident biological effects in sequential exams generating cumulative doses. In this regard, we cannot ignore the longer life expectancy of young subjects that probably will be exposed to several IR sources (including CT exams) during their lifetimes. On this matter, the role of radiologists, professors and researchers is to recognize the potential risks and demonstrate technical expertise to minimize them as far as the benefits are equally maximized, mainly for the more sensible population: children and adolescents.

Concluding remarks

Although it is clear that CT examinations cause DNA DSBs, which may lead/contribute to adverse health effects in patients, data about CBCT are limited. For 2D dentomaxillofacial radiographs, data are available, albeit that one may need to consider some methodological weakness biasing the results. Most data focusses on genotoxicity and cytotoxicity, but it might be interesting to look further at underlying mechanisms by using gene expression assays or by looking at specific proteins and their response to low doses of IR.

Furthermore, there is a lot of variability in the way radiation doses are reported. Some authors reported (estimated) effective doses, others reported absorbed doses or DLPs and even DAPs were used. This makes it very difficult to compare between studies and interpret the relative input. Therefore, it might be of interest to report doses in a standardized way, for example reporting absorbed dose or DLP. These two are least likely to be debated, since they can be measured accurately.

Also, the use of non-invasive detection methods, such as from saliva collection, to investigate the biological effects of medical and dental diagnostic procedures would aid to answer the encountered uncertainties.

Moreover, a lot of advancements are made in biomedical science (*e.g.* next-generation sequencing). These will allow to perform more high-throughput analyses and gather a lot of genomic/proteomic information, which is now often neglected in this type of studies. Therefore, more in-depth studies, such as gene expression analysis or next-generation sequencing, can give more insight in the consequences of the genotoxic insults described above as well as increase our understanding of the potential health risks associated with medical and dental diagnostic procedures.

Finally, clinical studies that include both adults and children are lacking. Therefore, not a lot of information is available about differences in response to IR between these age categories; this warrants further investigation. It is important to gain insight in potential age-related differences in effects of medical diagnostic procedures as it is vital to be able to properly assess the correct diagnostic tool at each age. In addition, radiation effects and radiation sensitivity are gender-specific. Existing epidemiological and experimental data suggest that radiation sensitivity in the long run is much higher in females than in males receiving a comparable dose. In accordance, recent studies observed an increased cancer risk in (young) females when compared to (young) males when exposed to CBCT.[28,33] To complicate things even more, radiation sensitivity also differs from one individual to another as also observed by our group in saliva samples of CBCT exposed children.[60] In accordance with the concept of personalized medicine, there is a need to consider the individual factor in the radiation response by taking age gender and other individual radiosensitivity-related factors into account. In this way,

radiation sensitivity and radiation-related disease risk can be better evaluated. Ultimately, these insights on the basis of individual radiation responses rather than on population averages of organ tolerance can contribute to improved radiation protection guidelines, which, in the end, will benefit the patient.

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