Chapter

Assessment of Occupational Exposures in the 3D Printing: Current Status and Future Prospects

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Abstract

3D (three-dimensional) printing technologies are widespread and rapidly evolving, creating new specific working conditions, and their importance has been highlighted by increasing publications in recent years. The report provides a compilation of current information on 3D technologies, materials, and measurements, considering the determination of the potential actual exposure dose of chemicals through airborne inhalation and dermal exposure, including workers' exhaled breath condensate and urine data. Noninvasive assessment methods are becoming increasingly popular, as they are painless, easy to perform, and inexpensive. Investigation of biomarkers reflecting pulmonary inflammation and local and systemic oxidative stress in exhaled breath, exhaled breath condensate, and urine are among them. It is also important to consider the occupational health and safety risks associated with the use of various new materials in 3D printing, which are associated with skin irritation and sensitivity risks. Therefore, EDI (estimated daily intake) calculations for assessment of the potential occupational health risk purposes *via* inhalation and dermal exposure are critical in future. The assessment of occupational exposure and health risks of 3D printing processes is essential for the proper identification, control, and prevention of working conditions, also for the diagnosis and monitoring of occupational diseases among workers to improve public health and well-being in general.

Keywords: additive manufacturing, 3D printing, occupational exposure, exhaled breath condensate, dermal exposure, biomarkers, exposure assessment, health risk evaluation

1. Introduction

3D (three-dimensional) printing has become an integral part of today's market and service industry since the 1980s, producing versatile and widespread products

not only in industry but also in the home. Nowadays, highly specialized industries, such as medicine, automotive, military, and aerospace engineering, use 3D printing for prototyping and facilitating the manufacturing process. Originally, the first material used was synthetic plastic, but as printing techniques have evolved, materials such as metals (steel), conductive materials, glass, ceramics, wood as well as organic tissue are also used. Besides, if 3D printing is combined with nanotechnologies, the future is under development, making it possible to create objects at nano and molecular level. One of the main type of emissions from desktop 3D printers is ultrafine particles (UFP), whose uniform distribution is related to the end of the printing process. In addition, about 50 different volatile organic compounds (VOC) have been identified from printer cameras of which the three most commonly emitted are styrene, caprolactam, and lactide [1]. Emissions occur especially when polymers are thermally treated. In general, exposure to contamination occurs *via* inhalation, food and beverage, water consumption, and dermal contacts. 3D emission main exposure routes are inhalation and dermal exposure, and usually, employees could be exposed at highest levels due to operations and maintenance of 3D printers, for example, when using acrylonitrile butadiene styrene (ABS) and polylactic acid (PLA), the worker is already exposed to emissions at an exposure time of 1 h [2]. Exposure *via* inhalation is breathing in a substance as a gas or vapor or as airborne particles. This includes small amounts of soil and dust that can be inhaled into the lungs. The lungs often absorb gases and vapors quickly and efficiently. Hereabouts, the estimated daily intake (EDI) for a chemical contaminant can represent the total exposure from all known or suspected exposure pathways for an average person to consider also their occupational exposures.

One of the possible methods to improve occupational health and safety in the 3D printing process to limit the spread of emissions is to seal heating, ventilation, and air condition systems with high-performance filters impregnated with activated carbon; to use a portable air purifier in the immediate operating areas; to install ventilation systems and enclosures in the emerging operating area for the storage of finished products [3]. Thus, ensuring local shock ventilation is an essential aspect of occupational safety. Furthermore, metal powder materials are at risk of ignition and it is recommended to use EX-devices (detection devices for explosive atmospheres) to identify the risk of explosion at workplaces [4].

Organizations (e.g., National Institute of Occupational Safety and Health (NIOSH), Occupational Safety and Health Agency (OSHA), etc.) with an objection to maximizing health protection from exposure to contaminants play an important role in identifying health risks and controlling emissions. Thus, NIOSH is a part of the Occupational Safety and Health Research of the United States of America. NIOSH's operational goals include understanding the health risks of advanced materials and manufacturing processes; studying the initial risks of engineered nanomaterials, advanced materials, and additive materials; supporting the development of guidelines and epidemiological studies to inform stakeholder identification of health risks and assessing progress to date; and evaluating risk management [5]. Further, OSHA's main focus is safety, health, and productivity of European workplaces, while promoting risk prevention and improving working conditions in Europe [6]. Working with 3D printers, existing occupational chemical risks compromising immune system function (cytokines-interferon and lymphokines), which play a key role in providing inflammatory responses and monitoring other abnormal processes. Considerable awareness of complex health assessment—cardiovascular, nervous, reproductive, etc. plays a role in the emergence of health risks and efficiency of occupational hazard

controlling and risk prevention [7]. In addition, well-being and productivity could be affected by poor working conditions caused by 3D printing activities at work, schools [8], and homes as well [9].

This chapter takes a complex look at the safety aspects of work-associated risks of 3D printing technologies.

2. 3D printing technologies, materials, and methods

Basic computer skills are needed for semiprofessional or home office printer users, while technicians also need knowledge to use 3D printers (in professional use). These printers come in different shapes, sizes, and prices—home office printers can fit on an office table but office or professional printers require a lot more space and it is suggested to keep them in a separate room (to limit noise and emission exposure) [10]. In order to attain the proper design goals, the materials in this special process must be functional. Material properties are highly important as the product undergoes conversion from design and functional prototype development to production [11].

Materials and technologies are a subject of constant improvement and modification, but the main and most commonly used materials and methods in 3D printing technologies will be discussed in the following chapter.

There are multiple industrial 3D printing processes: stereolithography (SL), powder-bed fusion (PBF), fused-deposition modeling (FMD), laminated object manufacturing (LOM), and direct energy deposition (DED) [11]. Each of these processes uses a different technology to produce the desired outcome. And each of them has many modifications, improvements, and varieties.

2.1 Stereolithography (SL)

Materials used in SL are usually photopolymers, and thermoset resins improved by ultraviolet (UV) light. There are numerous plastics that can be printed in 3D and have a variety of mechanical properties. SL is a fine-resolution and high-quality process commonly used in biomedical prototyping, yet the materials are quite scarce because of the relatively sluggish and expensive printing [11].

2.2 Powder-bed fusion (PBF)

PBF processes utilize tightly packed layers of ultra-fine powders on a platform. The polymer powder layers are fused together with a laser beam or a binder [12, 13]. Despite high cost, slow printing, and layer-by-layer finish, due to its high resolution and high-quality outcomes, PBF is a method that is widely used in a variety of industries, for example, biomedicine, electronics, aerospace, and to produce lightweight structures (lattices) [13].

2.3 Fused-deposition modeling (FMD)

In FMD, a continuous filament of thermoplastics and fiber-reinforced polymers are used. The thermoplasticity of the filament is crucial for FDM, allowing the filaments to fuse together during the printing process, and afterward, usually, a copolymer is used to solidify at layers. Due to its qualities and the materials used, FDM is a low-cost and high-speed prototyping method [14].

2.4 Laminated object manufacturing (LOM)

LOM can be used for a variety of materials, such as polymers, ceramics, paper, and metals. The printing method is based on layer-by-layer cutting and lamination of sheets or rolls, or the other way around. Reduced tooling and manufacturing time, a vast range of materials, and low cost allows to produce large structures and use for foundry industries, paper manufacturing, as well as in electronics and printing smart structures [11].

2.5 Direct energy deposition (DED)

DED method is also known as laser-engineered net shaping (LENS) and it is used to melt a feedstock material simultaneously. The melted material is then deposited and fused into the melted substrate and solidified after the movement of the laser beam [15]. This method is commonly used for stainless steel, Inconel, or with titanium, aluminum, and related alloys [11] and can be used for producing materials for repair, aerospace, biomedicine, etc.

2.6 "Hobby-class" 3D printing

3D printers are becoming more popular to be used at home as well, especially some portable low-cost desktop 3D printers (called "hobby-class"). In particular, the emergence of inexpensive portable 3D pens in the private and school sectors, using materials, such as PLA and ABS, is of concern due to the lack of data confirming their safe use [16].

Very few reports are available, which conclude a biosafety assessment of the 3D printer emissions, particularly the ones popular among young age users, such as 3D printing pens [17, 18].

However, a recent study has highlighted the potential risk posed by high particle emissions, including thermoplastic material nanoparticles as well as metal emissions from 3D pen usage [18].

3. Emissions from materials in 3D printing

All the above-mentioned methods use a variety of materials to produce the desired outcome products. The printing process uses high-temperature and the treated material emits VOCs, such as styrene, aldehydes, ethylbenzene, xylenes, caprolactam, lactide, and others, as well as UPFs [19–21]. It is known that ABS filaments are more hazardous to human health than PLA filaments. These emissions of particles and gases are higher when using ABS. ABS filaments produce VOCs, for example, styrene is a possible human carcinogen, but nylon filaments emit a compound called caprolactam (**Table 1**), which can lead to irritation of eyes and respiratory system and may cause effects on central nervous system. The total emission level and composition of VOCs depend on the filament material. PLA filaments have lower particle and total VOC emission rates than ABS and nylon filaments. There are some carbon emissions from the fumes when printing with polyethylene terephthalate glycol (PETG), and the main emitted VOC is acetaldehyde [29].

Some 3D printers use photopolymers (photosensitive liquid resins that become solid after exposure to laser or UV light) that are known to be toxic. During 3D metal

Filament	Type of VOCs	Reference
ABS	Aldehydes, acetone, diethyl phthalate, ethylbenzene, styrene, xylenes, etc.	[14, 22–27]
PLA	Acethyladehyde, butadiene, propionic acid, toluene, etc.	[28, 29]
NYLON	Caprolactam	[14, 26]
PETG	Acetone, ethylbenzene, formaldehyde, toluene, xylene, etc.	[15, 30, 31]
nGEN	Ethylbenzene, heptane, toluene, xylene, etc.	[31]

Table 1.
Some examples of emitted types of VOCs drives from some filament material used in 3D printing.

printing fine (including ultrafine) metal powder is used that is capable to become a respiratory hazard. Not only chemical risks but also well-known occupational health risks: high temperature, low humidity, high CO_2 levels, forced posture, eyestrain, and injuries can pose health risks among 3D printers' workers [32].

Depending on their content, other filaments may content additional chemical and metal exposures. The decision must be emphasized before using a particular type of filament, including 3D printers in the working environment. Considering the growing adoption of 3D printing and the growing mix of print materials with complex chemical properties, it is important for manufacturers to better educate themselves on the health risks to protect workers in their facilities [28].

UFPs may be of particular importance for the toxicity of fumes emitted from the melting of some thermoplastics [31, 33], although the latest literature reports show the release of UFPs and VOCs during printing with printers using nGEN (made by ColorFabb from Eastman Amphora™ AM3300 polymer) filament as well [31].

4. Occupational exposure

4.1 Risk identification

Occupational exposure data characterizing and description (e.g., profile of workplace, location, materials, equipment, methods, exposure time, ventilation, personal protective equipment, etc.) is an important issue to evaluate potential exposure, control, and prevention.

Furthermore, working environment description is essential to evaluate occupational exposure. The first step is to determine the exposure routes. During 3D printing process, workers can be exposed through inhalation or skin contact to various pollutants that can affect health and work abilities, oral exposure is less common in this industry. Also, to evaluate occupational exposure risk, 3D printing methods have to be categorized to determine the right pollutants in air in the previous paragraph. ISO standard defines 3D printing methods into seven categories: material extrusion, material jetting, binder jetting, sheet lamination, vat photopolymerization, bed fusion, and directed energy deposition [34].

During risk assessment and exposure determination, printing materials must be evaluated as well. In addition, exposure to printing materials, particulate matter (PM), and various chemicals can happen during cleaning and maintaining 3D printers and workspace. The common approach, for clarifying potential chemical substances' emissions of used materials and other agents during cleaning, maintenance, etc., is to check a chemical products safety data sheet [35].

4.2 Toxicity and health effects

As it is a new industry, only few publications indicate adverse health effects associated with 3D printing processes. One article mentioned that exposure to material extrusion fumes causes asthma [36]; however, other case reports mentioned chronic hypersensitivity pneumonitis with exposure to PBF nylon powder [37]. Various articles that used health questionnaires found a high incidence of 3D operator self-reported respiratory symptoms [38]. Animal studies show pulmonary and systemic toxicity in rats following exposure to 3D printing process [17, 39]; however, human studies on volunteers exposed to 3D printing fumes showed no acute changes in inflammatory markers [40]. Nevertheless, all this information draws attention to the risks of 3D printers.

Studies involving real occupational exposure measurements in 3D industrial settings are limited; however, the emission of material extrusion 3D printing process has been studied extensively, but the impact from other 3D printing technologies has not been documented as comprehensively. Emission and exposure in a work environment depend on differences in printing methods and related activities, including print materials. The thermal 3D printing process is a known source of VOCs and semi-volatile organic compounds (SVOCs). The typical VOC emitted during 3D printing can attach to airborne particles [41]. In addition, 3D printing is a source of UFP emissions [42–45].

VOCs and UFPs both have the potential adverse effect on human health through inhalation and skin contact, causing irritation, inflammation, lung disease, and various skin problems. It can also affect the central nervous system [36, 38, 46]. In addition, UFPs can pose health risks in a delayed manner even 1–5 days because of UFPs airborne exposure lag time. And UFPs toxicity depends on smaller size, larger surface area, absorbed substances, and physical properties [47]. Nowadays, 3D printing includes also nanomaterial usage in filaments because of their physicochemical and microbiological properties [48]. Further exposure measurements and the development of an appropriate measurement strategy for specific printing methods are needed to determine full exposure during the 3D printing process.

4.3 Prevention

The main principles of control/prevention measures at workplaces are elimination, replacement, technical, organizational measures, and personal protective equipment.

- Elimination of emissions or substitution with other materials.

- Technical measures that prevent emission sources. The most effective measure is a protective barrier for the emission source, closed-production systems are used and employees are physically isolated from contact with emissions. However, the potential for leakage with these activities should be considered. A mandatory requirement is the existence of local and general ventilation with special air filtration systems (e.g., HEPA) that retain dust, as well as forced exhaust systems.

- Organizational measures are the main measures to reduce risk. Employees' workplaces can be isolated, separated from the place where the process of 3D printing takes place. Isolation can take place, for example, by installing and creating walls.

- Personal protective measures: This control measure would be the last resort. Respiratory protection requires respirators and masks with filters or full-face or partial-covering masks with carbon filters, etc. [49, 50].

5. Exposure measurements and assessment in 3D printing processes

5.1 General data

In order to evaluate the exposure of the working environment of 3D printing, air sample analysis of the working environment is performed to determine the chemical composition (PM, VOCs, metals, and inorganic elements) and thermal comfort parameters (air temperature, humidity and air velocity) as well. Samples are taken in the breathing zone of the worker (i.e., within a radius of 30 cm around the face) to assess worker exposure or as close as possible to the workplace under normal working conditions. As it is listed and described into several technical standards and methods [51–54]. Main principles of measurement/sampling include purpose of measurement/sampling; selection of measurement/sampling location; selection of measurement/sampling technique; duration of measurements/sampling; selection of parameters to characterize worker exposure and potential health effects. It is important to consider the type of technologies, materials used during production and work processes, which allow us to guess what kind of chemical emissions could be released in the work environment. Measurements/samples should be taken in all work areas, where the work is performed [55].

Measurements done for risk assessment are a combination of traditional industrial hygiene methods and newly developed sampling techniques. Traditional methods include personal and area air sampling for the total PM concentration, inhalable dust [42, 45], respirable PM [43, 44, 56], VOCs or other potential exposures of interest [57]. Other exposure limit detection is done using direct reading instruments for PM count, sizing, and classification. Techniques used for this are condensation particle counters (CPC), optical particle counter (OPS), dust trackers, nano-scans, fast mobility particle sizer (FMPS™), electrical low-pressure impactor (Dekati® ELPI®+), etc. [56].

In addition, air temperature, relative air humidity and air velocity play a role regarding occupational exposure and employees' thermal comfort. Increasing air temperature also increases the emission of VOCs, as well as increases breathing rate and occupational exposure risk *via* inhalation as the main exposure route. And these parameters are influenced by outdoor conditions, premises' occupants, activities, etc. [58, 59].

5.2 Dust measurements

To determine the total PM concentration or inhalable dust in the breeding area of workers, personal samplers (plastic cassettes with filters inside of them) are used. During the measurement process, samplers are connected to air pumps with an airflow of 1.0 to 2.5 L/min. For the respirable dust level measurements, use the same type of air pump, but with a cyclone and membrane filter. Air flow for respirable dust measurements is from 2.0 to 3.0 L/min. Analysis of respirable or total PM concentration is done gravimetrically [42, 43, 60–62]. Individual work processes to calculate an 8-hour (shift) exposure level. The duration of measurement/sampling should reflect the real situation at the workplace, which includes all work processes that can cause the emission of chemical substances into the air of the working environment. But "not overloading" the samples with dust, especially if it is necessary to further use these samples

for the analysis of the chemical and physical characterization of aerosols. Work intensity and visual assessment of the work process allow one to choose the duration of sampling in non-emitting processes. The duration of the measurements depends on the homogeneity (uniform dispersion) of the pollution in the working environment. The inhomogeneous occupational environment precedes the longer measurements providing procedure (preferably the entire shift) and includes all processes.

Particulates in 3D industry are measured using direct reading instruments to determine particle size, count, and distribution, for example, Dekati® ELPI®+. And Dekati® ELPI® + measures during 3D printing show occupational exposure from $4x10^3$ to $26x10^3$ particles/cm^3 during 8-h shift. Furthermore, in all tested premises, the median diameter for particle number were detected: 0.014, 0.015, and 0.019 μm, but for mass concentrations: 4.394, 4.433, and 4.677 μm [46].

A condensation particle counter is used to measure the total number of particles with diameter from 10 to 1000 nm depending on the CPC model. An optical particle counter is used to measure the distribution of larger-size particles, usually from 1 to 10 μm, depending on the OCP model, as well as scanning mobility particle sizer is used to measure the distribution of particles. Using these techniques, particle surface area and volume concentration can be calculated from the measured number distribution assuming that particles are spherical; however, research showed trough 3D printer particle imaging it is not the case, as particles can be in different shapes [63, 64], this could lead to uncertainty in analyses [14, 42, 43].

5.3 Chemical measurements

The VOCs in 3D printing processes are done using traditional techniques with slight modifications. Measurements are done using adsorbent tubes Tenax TA type to capture VOCs or SVOCs; tubes are connected with sampling devices with airflow from 50 to 200 ml/min. After sampling, tubes are analyzed using gas chromatography (GC) with flame ionizing detector (FID)/mass spectrometry (MS) detectors [44, 65, 66]. Thus, in 3D printing offices, total VOC concentration was found at high concentration in comparison with indoor air quality recommendations, in general. In addition, there were estimated specific substances, such as toluene and formaldehyde, with concentrations 0.56 ± 0.1 and 0.23 ± 0.034 mg/m^3, respectively [46].

Passive sampling method to determine VOCs also can be used for monitoring purposes and in restricted areas, for example, drug development facilities, where 3D printing is used or in public buildings, for example, schools [67, 68].

Studies involving occupational exposure measurements in 3D industrial settings are limited. As emission and exposure in work environments depend on differences in printing methods and related activities, including print materials (also nanomaterials), further exposure measurements and the development of an appropriate measurement strategy for specific printing methods are needed.

6. Potential health effects and biomarker detection

6.1 Health surveys

In the scientific literature, questionnaires for the assessment of health disorders of employees working in the 3D industry have not been widely used. In 2016, Chan et al. conducted a survey of 17 companies in Toronto, Canada, surveying 46 employees, who

work daily in 3D printing companies [38]. The questionnaire included demographic information, work/ exposure, and symptom/ health history. The work/exposure section included questions about working hours per week, exact job descriptions and duration ratio, materials, and personal protective equipment used when working in 3D printing. The symptom/health section asked about previous diagnoses and whether they were aggravated by working at the 3D printing company, as well as their smoking status. If the employees noted that they tend to feel unhealthy during work, they were also asked about various symptoms and their frequency. Sixty-five percent (65%) of the surveyed employees experienced some symptoms more than once a week in the past year. In 59% of cases, employees noted various respiratory symptoms, 17% headaches, and 20% skin problems. Thirty percent (30%) of the respondents had already had some respiratory or skin diseases in the past prior to their work with 3D printers. Fifty-two percent (52%) of the surveyed employees admitted that they do not use any personal protective equipment during their daily duties [38]. Guemperlein et al. conducted an experimental study with 26 healthy volunteers. Each participant spent 1 hour in a special exposure chamber near the working 3D printer, approximately 40 cm away from the face. Before exposure, samples of urine, exhaled CO, nasal secretion, FeNO, and spirometry were taken. Immediately after exposure, volunteers completed a survey, repeated FeNO, urine sample, and spirometry. After 2–3 hours, another urine sample, FeNO and nasal secretion were taken. Participants were assessed for chemical sensitivity before entering the study by the chemical and general environmental sensitivity (CGES) questionnaire. After the exposure, the participants filled out a questionnaire noting their subjective feelings during the exposure. The survey had two sections: general feelings and a specific offer of symptoms, to determine the specifics of the experience. Proposed symptoms included various respiratory system disorders, skin and eye irritation, and headache. A visual analog scale (VAS) of 1–10 cm was offered for each of the variants. Most often, participants noted irritation in the nose and throat, eye fatigue, and headaches [40]. Two more studies are available where individual complaints after working with 3D printers are studied. House et al. have described a relapse of asthma after a 20-year hiatus in a 28-year-old businessman who had previously experienced a last asthmatic episode at age 8 [36]. Creytens et al. described an episode of allergic contact dermatitis of two 3D printing company workers [69]. The complaints of these employees are collected individually.

6.2 Noninvasive methods for health effect assessment

Noninvasive healthcare technologies are an important part of research and development today because they are cost-effective and offer benefits to both healthcare recipients and providers.

Various strategies are available to study the association between air pollutant inhalation and human health effects, the most promising of them is using noninvasive painless tests relatively simple in sample collection. Investigation of biomarkers reflecting pulmonary inflammation and local and systemic oxidative stress in exhaled breath condensate (EBC) and urine are among them.

6.2.1 Exhaled breath condensate (EBC)

The collection of EBC is a completely noninvasive method for obtaining samples from the lungs. EBC is a matrix containing numerous biomolecules, including nitric oxide-derived products, hydrogen ions, hydrogen peroxide, prostaglandins, and

leukotrienes. The sample collection is easy to perform, does not require special training of the participant, and has no influence on airway function or inflammation. EBC is obtained when the breath is exhaled from the lungs into a cooled collecting device; thus, condensing the vapor. In terms of biomarkers, determination in EBC focus must be put on the temperature in the cooling device and freezing of the samples due to the presence of chemically unstable substances (e.g., leukotrienes).

Information relating to some detectable biomarkers in EBC is provided below in **Table 2**.

6.2.1.1 Acidity and nitrogen/oxygen species

Assessment of EBC pH for detection of airways acidity purposes is widely described in research studies and it is related with airways inflammation [24, 84, 85]. Low EBC pH is found in patients with a variety of inflammatory lung disorders, including cystic fibrosis, chronic obstructive pulmonary disease (COPD), and asthma [84]. Acid stress can also be used to understand the effect of environmental

Biomarker (s)	Detection method/ Measurement device	Benefits/ Drawbacks	Subjects, range	Year, Ref.
Acidity and nitrogen/oxygen species				
Acidity (pH)	pH was recorded with a calibrated and validated glass microelectrode on stabilization/glass microelectrode.	Simple, quick, easy to perform, and highly reproducible.	404 healthy subjects, all ages, mean value 7.83, median value 8.0 (7.7–8.1), no differences based on age, sex, or race.	2007, [24]
NO_2/NO_3	Commercially available colorimetric assay kit, LOD 1 mcM/spectrophotometer, microplate reader.	Low values in healthy subjects; samples need concentration.	15 healthy controls; age 39 ± 10 (M6/F9); NO_2 < 1 mcM NO_2/NO_3 11.4 mcM	2005, [70]
NO_2/NO_3	Nitrate is measured as nitrite after enzymatic conversion by nitrate reductase using Griess reagent; LOD till 1.0 mkM/ spectrophotometer.	Complicated, long preparation, but informative.	10 normal, nonatopic subjects; age 23 ± 4 (males); NO_2/NO_3 0.63 (0.20-0.41) mcM;	2001, [71]
H_2O_2	Enzymatic assay; LOD 0.1 mkM/ double beam spectrophotometer.	Low values in healthy subjects.	10 normal, nonatopic subjects; age 23 ± 4 (males); H_2O_2 0.3 (0.2-0.4) mkM	2001, [71]
H_2O_2	The fluorescence of the reaction product (dimer 2,2'- dihydroxybiphenyl-5,5'-diacetate) measured with an automated sampler, low injection, and scanning fluorescence detector (295/405 nm); LOD 0.02 mcmol/L; fluorimeter with automated sampler.	Reproducible; H_2O_2 concentration in most healthy persons is below the LOD.	20 stable chronic obstructive pulmonary diseases (COPD) patients; no healthy subjects.	2002, [72]
NO_2/NO_3	Colorimetric assay based on the Griess reaction; LOD 2.5 mcM/ microplate reader at 540 nm.	Relatively simple; good variability.	20 healthy nonsmokers, age median 60 (52–73); NO_2/NO_3 15.06 (10.73–23.30) mcM.	2010, [73]

Biomarker (s)	Detection method/ Measurement device	Benefits/ Drawbacks	Subjects, range	Year, Ref.
3-Nitrotyrosine	A specific enzyme immunoassay (EIA) (Cayman Chemical, Ann Arbor, MI, USA); LOD 3.9 ng/mL/ freeze dryer for concentration.	Low values in healthy subjects; sample concentration is necessary.	14 nonsmoking healthy volunteers (6 male), age 34 ± 2 yrs.; 6.3 ± 0.8 ng/ mL.	2001, [74, 75]
Nitrosothiols (RS-NOs)	Commercially available colorimetric assay kit (Oxonon, Emeryville, CA) based on classic reaction of Saville and Griess; LOD kit 0.025 mcM/ spectrophotometer, microplate reader, at 540 nm.	Relatively easy to perform. Low values in healthy subjects.	Nonsmoking control subjects (n = 10), age 30.2 ± 1.5 yrs.; smoking control subjects (n = 7), age 36.1 ± 3.2; 0.11 ± 0.02 mcM;	2001, [75]
Eicosanoids (prostaglandins and leukotrienes)				
Cysteinyl-leukotrienes (cys-LTs: $LTC_4/D_4/E_4$); leukotriene B_4	Specific enzyme immunoassay (EIA) kits; LOD: cys-LTs 15 pg./mL; LTB_4 4.4 pg./mL.	Relatively easy to perform. Expensive, high variability.	15 normal controls; age 32.3 ± 4.5 (7 male); cys-LTs 15.5 ± 0.2 pg./mL; LTB_4 63.1 ± 17.3 pg./mL	2000, [76]
cysteinyl-leukotrienes/ prostaglandin E_2/ leukotriene B_4	Specific enzyme immunoassay (EIA) kits (Cayman Chemical, Ann Arbor, MI); LOD: cys-LTs 13 pg./mL; PGE_2 15 pg./mL; LTB_4 4.4 pg./mL	Relatively easy to perform. Expensive	16 healthy subjects; age 45 ± 17 yrs.; cys-LTs 19.4 ± 2.8 pg./mL; PGE_2 and LTB_4—no information	2002, [77]
8-iso-prostaglandin $F_{2\alpha}$	Competitive enzyme immunoassay kit; sensitivity 4 pg./mL/Specific reader	Variable (CV 11–15%)	Healthy nonsmokers, n = 20; age median 60 (52–73); 9.09 (6.63–11.43) pg./mL	2010, [73]
8-iso-prostaglandin $F_{2\alpha}$	Solid-phase extraction using liquid chromatography-electrospray ionization-tandem spectrometry (LC-ESI-MS/ MS); LOD 1.2 ± 0.2 pg./mL	Precise. Long; expensive; requires expensive instruments.	21 healthy controls (15 male); age 38.7 ± 9.1 yrs.; values not presented, only comparison	2020, [78]
Inflammatory mediators				
Cytokines interleukin (IL)-1β, IL-4, IL-6, IL-8, IL-10, tumor necrosis factor-alpha (TNF-α), C reactive protein (CRP)	ELISA or cytometric bead array (CBA) assays, according to the manufacturer's guidelines; need normalization to protein concentration/ specific device (e.g., Randox evidence).	Cytokine concentration is around the assay LOD; high variability; expensive; depends on the assay kit manufacturer.	CRP 0.075 ± 0.03 mg/L; IL-1β 3.31/3.74 pg./mL; IL-4 31.6–40.8 pg./mL; IL-6 2.6–5.2 pg./mL; IL-8 3.15–16.3 pg./mL; IL-10 1.0–24.3 pg./mL; TNF-α 0.4–4.84 pg./mL.	2022, review article [79]
Lipid peroxidation end products and damage to nucleic acids				
Malondialdehyde condensed with thiobarbituric acid (MDA-TBA)	HPLC with fluorescent detection (ex 532 nm/em 553 nm); LOD 4.1 nM	Relatively easy to perform; linear, selective. Samples stability: at −20°C 1 month; at −80°C 3 month;	Only patients; range 0.15– 0.23 pmol/s	2002, [80]

Biomarker (s)	Detection method/ Measurement device	Benefits/ Drawbacks	Subjects, range	Year, Ref.
Malondialdehyde condensed with thiobarbituric acid (MDA-TBA)	HPLC with fluorescent detection (ex 532 nm/em 553 nm); LOD 1.8 nM	Relatively easy to perform, linear, selective, precision 2.2%.	125 healthy adults, age median 24 (19–33); male/female = 64/64; 16.0–22.3 nM	2013, [81]
8-iso-prostaglandin $F_{2\alpha}$, malondialdehyde (MDA), 4-HNE - complex detection	Liquid chromatography-electrospray ionization-mass spectrometry/mass spectrometry (LC-ESI-MS/MS); LOD: 8-iso $PGF_{2\alpha}$ - 2 pg./mL; MDA – 21 pg./mL 4-HNE – 26 pg./mL	Pretreatment part: solid-phase extraction for biomarkers isolation from matrix; samples are spiked with biomarkers. Requires expensive instruments.	10 control subjects, age average 63 ± 5 yrs.; male/female similar; Median: 8-iso $PGF_{2\alpha}$ - 47 pg./mL; MDA – 43 ng/mL 4-HNE – 162 ng/mL	2009, [82]
8-hydroxy-2-deoxyguanosi-ne (8-OHdG)	Liquid chromatography-electrospray ionization-tandem spectrometry (LC-ESI-MS/MS); LOD 7 pg./mL.	High sensitivity and specificity, reproducible. Requires expensive instruments	Healthy individuals, 9.0–21.0 pg./mL	2022, review article [83]
	ELISA immunoassay; LOD 41 pg./mL / spectrophotometer or fluorimeter, microplate reader.	Simple, low cost; variable, less specific; not validated for EBC.	Healthy individuals, 360 ± 90 pg./mL	
4-hydroxynonenal (4-HNE)	4-Hydroxynonenal ELISA immunoassay kit; Sensitivity: 18.75 pg./ml Range: 31.25–2000 pg./mL. Spectrophotometer/ microplate reader.	Variable; not standardized for detection in EBC.	—	2022, [83]

Table 2.
Biomarkers in exhaled breath condensate (EBC). LOD—Limit of detection.

conditions on the airways. However, the presence of CO_2 in the samples interferes with the results and must be removed using deaeration or degasification as recommended by the European Respiratory Society technical standard [85] to avoid high variability of the results. pH values less than 7.4 are considered to be abnormal [24].

Production of nitric oxide (NO) is generally increased in inflammatory conditions, but it is difficult to measure because it is a free radical, which reacts rapidly with oxygen, superoxide, water, thiols, amines, and lipids to form products with biochemical activities, but nitrites and nitrates are products of nitric oxide metabolism, and these products can be detected in EBC. Investigators use different methods to assess nitrite/nitrate levels in EBC, examples are presented in **Table 2**.

Nitrotyrosine is formed when nitric oxide and superoxide anions create peroxynitrite, which can then react with tyrosine residues on proteins. Nitrotyrosine, which is formed in the airways, can be collected in the EBC and serves as a marker of oxidative stress. Increased production of nitrotyrosine may reflect the increased formation of reactive nitrogen species, such as peroxynitrite in airways and also in the whole

organism. Some investigators consider that nitrotyrosine formation in EBC may be a more sensitive marker to evaluate the contribution of oxidative stress to airway inflammation than exhaled NO [76, 86].

Nitrosothiols (RS-NOs) are formed by the interaction of nitric oxide with thiol-containing macromolecules (glutathione and cysteine) and may limit the detrimental effect of NO. RS-NOs are detectable in EBC of healthy subjects and of individuals with various inflammatory airway diseases. Increased levels of RS-NOs may be related to enhanced nitrosative stress. A positive correlation between smoking history (packs/year) and RS-NOs levels suggest that nitrosative stress induced by smoke stimulates RS-NOs production, and also indicates that RS-NOs can be used as a biomarker of ambient air pollution and pulmonary nitrosative stress [76].

Exposure to exogenous oxidants, such as inhaled cigarette smoke and/or air pollution, increase oxidative stress in exposed individuals. The degree of oxidative stress can be determined by measuring hydrogen peroxide (H_2O_2) concentration in EBC [71, 72]. Also, H_2O_2 is released by neutrophils and eosinophils and by macrophages and epithelial airway cells; it provides one line of defense against infection and is therefore an important marker of airway infection. Thus, measurements of H_2O_2 in EBC can be used as a maker of oxidative stress and/or inflammatory processes in occupational medicine (**Table 2**).

6.2.1.2 Eicosanoids (prostaglandins and leukotrienes)

Prostaglandins and thromboxanes are synthesized by the cyclooxygenase (COX) pathway in arachidonic acid cascade. Studies of the eicosanoid pathway and COX inhibition suggest that this biomarker may be used to understand processes of airway inflammation. The 8-iso-prostaglandin F2α (F2-isoprostane or 8-iso-PGF2α) is a lipid peroxidation product of arachidonic acid and the representative marker of oxidative damage. However, there is an alternate enzymatic pathway to generate 8-iso-PGF2α catalyzed by prostaglandin endoperoxide synthase, which is independent of free radical-mediated peroxidation. This fact can impact the conclusions based on the 8-iso-PGF2α increase concentration under exposed conditions reflect in literature analysis by Hemmendinger et al. [83]. So, measurement of only esterified 8-iso-PGF2α or total 8-iso-PGF2α, may be a more indicative marker of oxidative stress [83, 87]. Van 't Erve and coworkers provide a detailed literature meta-analysis of the levels of 8-iso-PGF2α in systemic oxidative damage across human disease and in response to environmental exposures and concluded that there is a general increase in the levels of both free and total 8-iso-PGF2α associated with mentioned conditions [88].

Cysteinyl-leukotrienes (cys-LTs) and prostaglandin E2 (PGE2) are eicosanoids implicated in the development of airway disease mechanisms [76, 77]. PGE2 relaxes airway smooth muscles and exerts potent anti-inflammatory activity. Activated eosinophils and mast cells are capable of producing several inflammatory mediators, including cysteinyl-leukotrienes (cys-LTs) (LTC4, LTD4, LTE4), which, in turn, are potent bronchoconstrictors.

Cytokines measurements in EBC are widely used as inflammatory biomarkers. The main cytokines with a pro-inflammatory role are interleukin (IL)-1β, IL-6, tumor necrosis factor α (TNF-α), and C reactive protein (CRP). Anti-inflammatory cytokines, instead, such as IL-4 and IL-10, play a crucial role in controlling the regulation of pro-inflammatory cytokines. Positive associations of these biomarkers with workplace aerosols, including nanocomposite materials, were reported [89].

Recently, a thorough literature systematic review was done by Ghelli and coauthors comparing baseline values of pro/anti-inflammatory cytokines measured in healthy, nonsmoking adults in order to elucidate issues that interfere with the obtained results evaluation: standardization of sampling and test preparation are the most actual [79].

6.2.1.3 Lipid peroxidation end products

Lipid peroxidation is a well-defined mechanism of cellular damage, lipid peroxides are formed under oxidative stress conditions and form more complex and reactive compounds, such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), which have been shown to be capable of binding to proteins and forming stable adducts—advanced lipid peroxidation end products. These products are generally accepted biomarkers of oxidative stress. Since oxidative stress has been recognized as an important mechanism by which air pollution exposure leads to adverse health effects, the positive association of lipid peroxidation product levels in EBC and air pollutants concentration was observed. Increased MDA-TBA was associated with fine particles of PM2.5, elementary carbon, and sulfur dioxide concentration [81]. The author's finding suggests that gaseous pollutants may lead to lipid peroxidation in the respiratory tract more rapidly than particulate pollutants. MDA is a marker of oxidative stress also in different pulmonary diseases [90]. The following analytical methods are used for MDA detection in EBC: high-performance liquid chromatography/thiobarbituric acid (HPLC/TBA), spectrophotometry/TBA, HPLC-mass spectroscopy (HPLC-MS), HPLC-MS/initrophenylhydrazine (DNPH) [91], but HPLC/TBA is considered the reference method (**Table 2**). Due to methodological discrepancies in sampling and detection technics, a reference interval in healthy adult populations for MDA in EBC is not established.

4-hydroxynonenal (4-HNE) measured in EBC was not significantly affected by systemic disorders, but was increased in patients with occupational respiratory disorders due to asbestos and silica expose; therefore, can serve as a good biomarker for oxidative stress [82, 92].

8-hydroxy-2-deoxyguanosine (8-OHdG) is commonly used for identifications of oxidative damage to nucleic acids. Two main analytical approaches are available for 8-OHdG: immunoassay-based methods (ELISA) and chemical analytical methods, such as gas or liquid chromatography with MS detection. 8-OHdG was found to increase the EBC of engineered nanomaterials exposed workers, smokers, COPD patients, and patients with occupational respiratory disorders due to asbestos and silica expose [82, 83, 93].

All above mentioned allow us to consider that in order to perform qualitative reproducible investigation/study of biomarkers in exhaled breath condensate it is necessary to work out elaborated sampling collection protocol according to the European Respiratory Society/American Thoracic Society recommendations, including participant training and total volume of air exhaled, select samples storage conditions, to choose more informative biomarkers with appropriate detectable methods and use standardized analytical protocols for sample preparing and analysis.

6.2.2 Biomarkers in urine

Biomarkers measurement in urine has many advantages: urine collection is noninvasive, can be obtained in large quantities, contains relatively low concentrations of metals and organic content, and can be stored for a long time. On the other hand, the

content of biosubstances in urine can be influenced by diet, there are some cells or cell debris, and bacterial growth can occur during urine storage.

The most commonly measured urine biomarkers in air pollution or occupational health studies are biomarkers of oxidative stress products: F2-isoprostanes, aldehydes in forms of MDA, 4-HNE adducts, 4-oxo-2-nonenal (4-ONE), DNA oxidation modification product 8-OHdG (**Table 3**).

Biomarker (s)	Detection method/ Measurement device	Benefits/ Drawbacks	Subjects, range	Year, Ref.
8-iso-prostaglandin $F_{2\alpha}$ (8-iso-PGF2α)	Commercial ELISA kit; Inter-assay precision: 0.53% to 6.08% Intra-assay precision 8%. LOD 16.3 pg./mL. Specific reader	Variable; cross-reactivity occurs	None-exposed group, Chinese N = 210; range 1.1–2.9 mcmol/mol creatinine	2021, [94]
	Gas chromatography-tandem mass spectrometry (GC-tandem MS); LOD 1.2 ± 0.2 pg./mL. Requires expensive instruments	Precise. Long; expensive; spiked samples	93 healthy controls (M/F 160/26); age 63.5 ± 7.9 yrs.; 80–130 pmol/mmol creatinine	2004, [95]
	Liquid chromatography-tandem mass spectrometry (LC-tandem MS). Requires expensive instruments.	Precise. Long; expensive; sample pretreatment; spiked samples	12 healthy men; 69.25 ± 3.81 yrs.; 103.38 ± 32.18 ng/mg creatinine.	2022, [96]
Malondialdehyde condensed with thiobarbituric acid (MDA-TBA adducts)	MDA-TBA adducts commercial kit Inter-assay precision: 0% to 2.02% Intra-assay precision: 0.12% LOD 0.5 nmol/mL. Spectrophotometer or fluorimeter, microplate reader	Relatively easy to perform; linear, selective	None-exposed group, Chinese N = 210; range 345.6–794 mcmol/mol creatinine	2021, [94]
	High-performance liquid chromatography HPLC with mass spectrometry (MS), fluorescence detection, or UV photometry;	Depend on the selected method; high heterogeneity	Healthy populations, 0.07–0.12 mg/g creatinine	2022, review [97]
8-iso-prostaglandin $F_{2\alpha}$, malondialdehyde (MDA), and 4-hydroxynonenal (4-HNE) - complex detection	Liquid chromatography-electrospray ionization-mass spectrometry/mass spectrometry (LC-ESI-MS/MS); LOD: 8-iso $PGF_{2\alpha}$ - 17 pg./mL; MDA – 87 pg./mL 4-HNE – 91 pg./mL	Samples pretreated and spiked with biomarkers. Long. Requires expensive specific instruments	10 control subjects, age average 63 ± 5 yrs.; male/female similar; Median: 8-iso $PGF_{2\alpha}$ – 24 ng/mmol creatinine; MDA – 6.8 mcg/mmol creatinine 4-HNE – 182 mcg/mmol creatinine	2009, [82]

Biomarker (s)	Detection method/ Measurement device	Benefits/ Drawbacks	Subjects, range	Year, Ref.
8-hydroxy-2-deoxyguanosine (8-OHdG)	Ultra-high-performance liquid chromatography-mass spectrometry (UPLC-MS/MS); LOD 0.5 ng/mL.	High sensitivity and specificity, reproducible. Requires expensive instruments	Healthy individuals, Chinese144; age < 45 yrs.; about 0.4 mcmol/mol creatinine.	2019, [98]
	Liquid chromatography-tandem mass spectrometry (LC-tandem MS). Requires expensive instruments.	Precise. Long; expensive; sample pretreatment; spiked samples	12 healthy men; 69.25 ± 3.81 yrs.; 1.87 ± 0.77 ng/mg creatinine	2022, [96]
	ELISA commercial kit; Sensitivity 0.59 ng/mL; LOD 41 pg./mL / spectrophotometer or fluorimeter, microplate reader.	Simple. Variable, less specific.	Healthy individuals, Body mass index >25; 5.9 to 19.8 ng/mg creatinine.	2020, review [99]

Table 3.
Biomarkers in urine. LOD—Limit of detection, F—Females, and M—Males.

F2-isoprostanes are the products of non-enzymatic oxidation of arachidonic acid by different free radicals, also the additional enzymatic pathway from esterified phospholipids not related to oxidative stress occurs [100]. There are 4 F2-isoprostane isomers presented and detectable in urine [101].

Three main techniques used to assay F2-isoprotanes in urine are gas-chromatography with mass spectrometry detection (GC-MS), liquid chromatography with tandem mass spectrometry detection (LC-MS/MS), and enzyme-linked immunosorbent assay (ELISA). Mostly, the measurements are assigned to 8-iso-prostaglandin F2α.

MDA is a frequently used biomarker that is measured in urine using different methods. Detailed analysis of urinary MDA levels for healthy adult populations is presented by Toto et al. [97]. MDA levels are evaluated after air pollution exposure [81]. However, some investigators pay attention to non-specificity of MDA formation in oxidative conditions and possible dietary, body mass index (BMI), and age as confounding factors, concluding that MDA cannot be recommended as a systemic biomarker of oxidative stress [101].

4-HNE and 4-oxo-2(E)-nonenal (4-ONE) are products of polyunsaturated fatty acids oxidation, highly reactive aldehydes, easily form covalent bonds with protein thiol and amino groups and with other biological molecules, so their levels are unstable [101], but measuring of their stable adducts is used as oxidative stress biomarkers. 1,4-Dihydroxynonane mercapturic acid (DHN-MA), the major urinary metabolite of 4-HNE, is an additional biomarker that may be assayed [102], and commercially available kits may be used. Another possibility is to use high-tech techniques, such as liquid chromatography/gas chromatography, in tandem with mass-spectrometry, depending on the study purpose [103, 104]. Measurements of urinary 8-OHdG include chromatography-based methods (HPLC MS/MS, HPLC ECD, GC/MS, etc.) and ELISA, with chromatography-based techniques showing low inter-assay variability,

but cross-reactivity and inter-individual variability for all [101, 105, 106]. Diet and cell death have minimal, if any, influence on urinary levels of 8-oxodG, but results may be age-dependent [107]. The pooled median value for urinary 8-OHdG concentrations in healthy adults with a mean BMI ≤ 25 measured using chemical methods was 3.9 ng/mg creatinine (range from 3 to 5.5 ng/mg) [99]. Increased urinary 8-OHdG was associated with air and work-place pollutants; however, data are contradictory [108].

In conclusion, it is necessary to pay attention to the standardization of urine sample collection (spot or 24-h urine), storage conditions (time and temperature), pretreatment of samples (urine is a very complex matrix), appropriate choice of biomarkers, results in creatinine normalization—the rigorous study design/protocol is essential to obtain repeatable reliable results.

7. Estimated daily intake (EDI) and health risk modeling

Pollutants pose a potential hazard to public healthcare, particularly human exposure. It is important to understand to what extent the population is exposed to environmental pollutants at work and home. It is important to track the level of environmental pollutants in the population, which allows an assessment of how exposure to pollutants in this population changes over time [109, 110].

Human contact occurs *via* inhalation, ingestion, or dermal exposure [111].

Different approaches are used to measure possible human exposure, for example, exposure modeling, personal monitoring, and ambient concentration measurements. Exposure models estimate exposure by combining information about environmental contaminant concentrations, including surveys about people's activities and locations (working shifts, exercising indoors/outdoors, sleeping, food consumption, etc.) to account for possible contact with contaminants [68, 112, 113]. As a possibility, exposure indices can be developed to evaluate relative changes in environmental contaminant exposure over time [113].

Biomonitoring measures how much a pollutant or its metabolites or reaction product—biomarkers—are present in the human body. Several environmental contaminants, for example, heavy metals, pesticides, and other organic pollutants, can accumulate in the body. Measurements are commonly made in blood and tissues obtained by biopsy or autopsy (invasive method) or using urine, feces, breast milk, hair, nails, skin contaminants, and exhaled air condensate (noninvasive methods) [114, 115].

Occupational hygiene practices have generally focused on the inhalation of exposure pathway. It was assumed that inhalation was the main route of exposure, with some exceptions (pesticides, certain solvents, etc.). Many methods have been developed to measure inhalation exposure and there is a clear idea of how to interpret these values in the context of a risk reduction strategy. Attempts have been made to reduce inhalation exposure over the years, and some authors have suggested that dermal exposure may be more important compared [116, 117].

7.1 Estimated daily intake (EDI)

Evaluation of the level of health and safety risk during 3D printing based on the data of the EDI calculation data [118].

Exposure by inhalation is the inhalation of a substance as a gas or vapor or as particles in the air. This includes small amounts of soil and dust that can be inhaled into the lungs. The lungs often absorb gases and vapors quickly and efficiently. We are all

exposed to low levels of contamination in the air we breathe, food we eat, and water we drink. The total exposure across all suspected exposure pathways for a chemical pollutant for an average person describes the EDI [111, 119–121]. The calculations of the EDI method are directly adjusted to the occupational exposure data for recommendations [38, 122–129]. The EDI value of chemicals can be calculated by adding up all. In summary, each EDI is the amount of pollutant absorbed through a different combination of exposure routes and exposure pathways (**Figure 1**).

All equations for calculating the estimated amount of the pollutant taken up *via* the combinations of exposure pathway and exposure route are similar, but require a different equation for each combination [130, 131].

Health risks from occupational dermal exposure to hazardous substances may also occur at many workplaces. In addition to the local effects that chemicals can directly have on the skin, the skin also acts as a pathway for hazardous chemicals to be absorbed into the body. The dermal dose absorbed is the amount of a chemical absorbed into the body through the skin [132]. In recent decades, several methods have been developed to assess dermal exposure. These methods can be broadly divided into direct (interception and sampling methods and visualization techniques) and indirect methods (surface sampling methods (nonhuman), dermal exposure modeling, and biomonitoring) [133, 134].

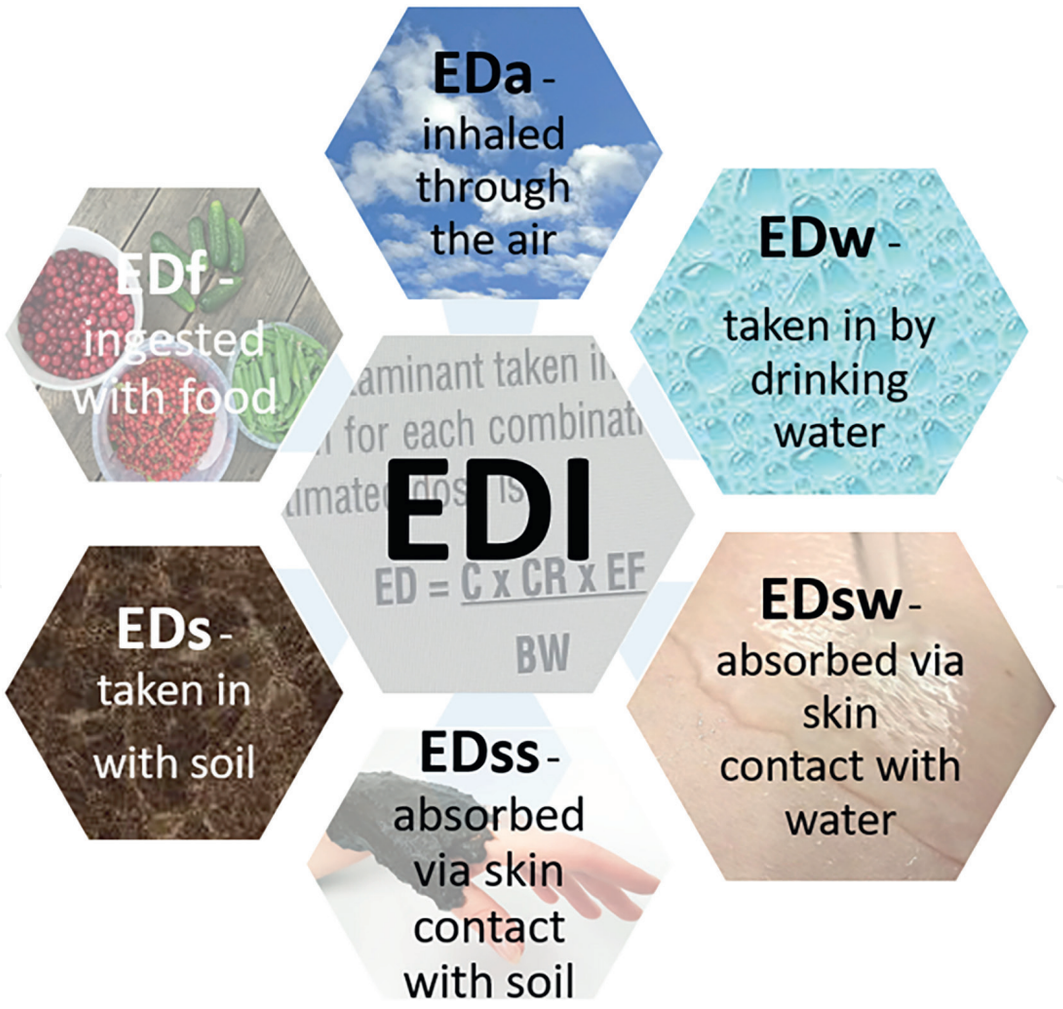

Figure 1.
Combination of exposure routes forming EDI.

The dose-response relationship is the relationship between the amount of a contaminant that is given and the health effect. It is possible to measure short-term exposure or exposure as a function of time. Exposure means contact of chemicals with the outer perimeter of an individual, for example, skin, nose, mouth, and doses. There are four ways to analyze dermal exposure that has occurred: the first is the potential dose, which is the amount of contaminant applied to the skin. The second, the applied dose indicates the amount of the pollutant at the absorption barrier (e.g., the skin) that can be absorbed by the body. The third and fourth doses are the internal dose (the amount of the pollutant that is absorbed and available to interact with biological receptors, e.g., organs and tissues) and the biologically effective dose (the amount of the pollutant that interacts with the internal target tissue or organ), respectively [135]. Depending on the exposure assessment, it may be necessary to assess the effects and dose in different ways [136]. Calculations of dermal exposure can be made as lifetime average daily potential dose (LADD), average daily potential dose (ADD), and acute potential dose rate (ADR). The potential skin dose rate can be determined by dividing the potential dose rate (PDR) by the body weight to obtain the normalized potential dose, with the body weight chosen to fit the specific population of individuals [132, 134, 137, 138].

Another important meaning is applied by governments to set guidelines that protect human health from the potential health effects of exposure to environmental pollutants: the tolerable daily intake (TDI). Acceptable daily intake (ADI) is also used interchangeably with TDI. However, the two terms TDI and ADI describe the same value. Guidelines for TDI are regularly reviewed and revised, especially when new scientific information on pollutants becomes available.

The TDI calculations depend on how comprehensive the studies (usually on animals) were and how confident the researchers were in extrapolating the data to humans.

For contaminants known to be carcinogenic, the risk-specific dose (RSD) is required. The RSD is the amount of contaminant to which people can be exposed daily throughout their lifetime without exceeding the accepted risk of cancer.

8. Future prospective for 3D printing risk assessment

The technology of 3D printing will alter how we create, produce, and distribute our consumer items in this digital age. In recent years, expectations for 3D printing have been so high that nothing less than a new industrial revolution has emerged. [139].

Food industry started using 3D printing opportunities because of food's flexible production and freedom in creation. For example, it is used for liquid food (chocolate, pancake batter, etc.) production [140]. The literature highlighted that the latest directions in the field of the 3D food industry are to introduce new bioactive ingredients in addition to basic nutrients. In nearest future, raw food also will be produced by 3D technologies next to heating, fermentation, or germination [141]. Therefore, it will arise new challenges regarding hygiene, safety, and working conditions (air quality, ergonomics, etc.), in general. This will present new difficulties for hygiene, workplace safety, and general conditions (clean air, ergonomics, etc.). The controlling of smart materials processing by temperature, power, light, moisture, pH, and electric or magnetic fields can change smart materials' properties, for example, changing shape, tactility, or hardness [142]. Thus, this transformation process leads to 4D printing because of material availability changes again over time. And these changes will be initiated by sensitivity to light, pressure, or temperature. Furthermore, some of

smart materials will have "a memory," when these materials can change back to their initial shape under the changing of circumstances again. Considering these types of materials' experimental stage at the moment, their impact on health and hygiene is uncertain [143]. There have been calls for regulation [144].

One of the potential challenges is to detect errors in 3D printing with the help of artificial intelligence. Brion et al. [145] proposed a multi-head neural network employing labeled pictures that allows for the detection of deviation from ideal printing settings and permits reliable and generalizable, real-time extrusion additive manufacturing mistake detection, and quick rectification.

Developing 3D printing of organic and/or living tissues is essential and very promising because of inserting cells into requested places. And this technology is based on bioprinters' head movements and cell insertion. Bioprinting will offer to create many very thin layers of tissues. Thus, algae and fungi already are successfully used in experiments to manufacture "living" materials, but same as regarding smart materials also "living" materials potentially could cause risks to health and hygiene. Furthermore, it raises ethical issues [146]. Also, nanotechnologies are combined with 3D printing to shape objects at nano or molecular size receiving opportunities through additive manufacturing to create any form, material, shape, or volume objects. However, this technology is still theoretical without a well-known nanoprinting effect on to work environment, in general [4].

Exposure assessment future perspectives based on accurate personal sampling, specific pollutants' assessment, and sensitive biomarkers' evaluation with a purpose of highlighting 3D printing emissions impact on employees' health. There are important existing sensitive methods (e.g., exhaled breathing condensate collection and analysis) and evaluation of health risk according to calculations approaches (e.g., EDI) implementation for occupational exposure assessment in 3D printing industry.

9. Conclusions

The growing popularity and widespread use of 3D printers raise concerns about their health effects. It is extremely important to identify the chemical substances released by the 3D printing process to more accurately determine the extent of exposure and assess potential health risks. The placement of the workplace where 3D printing is performed is also important, particularly a sufficiently efficient ventilation system, the technical condition of the 3D equipment itself, the materials used, and the amount of time the worker spends on the equipment. To assess the potential health effects of 3D printer emissions, information from safety data sheets and exposure analyses, including exposure assessment and dose calculations (e.g., EDI), can be used (adapted for specific occupational exposures, including 3D printing). Future prospects include sensitive and noninvasive biomaterial analyses to assess health risks, such as exhaled breath and urine biomarkers, for example, oxidative stress, etc. More research is needed to select the most appropriate biomarkers for risk assessment. As 3D printing technologies evolve, their emissions and the materials used also change, so it is important to continue their research and emission determination. Sensitive and appropriate methods, including equipment, for sampling and analytical analysis will be promoted and developed in the future. Hobby-class 3D printers (also 3D pen printing), which are most commonly used at home, are a separate issue because in most cases there is not adequate ventilation and controlled environmental conditions at home, especially if the users are children.

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