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Review

Safe Functional Modified CuO Nanoparticles?

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Abstract: CuO nanoparticles produced by methods from inorganic chemistry and physics are applied as biocides and applications thereof in solar stills, solar collectors, catalysis, sensing and diesel fuels have been proposed. Such CuO nanoparticles are hazardous due to the release of Cu ions and the induced generation of reactive oxygen species after uptake by organisms. Nanoparticle hazard may be reduced by surface modification (coating or capping) and doping which reduces the release of Cu ions and the generation of reactive oxygen species. None of the published safe-by-design modifications of CuO nanoparticles that will be discussed here have been proven safe (no risk). By targeting the release of Cu ions and the generation of reactive oxygen species by CuO nanoparticles, safe(r)-by-design studies target properties that underly the biocidal functionality of CuO nanoparticles. Other functionalities of CuO nanoparticles may also be impacted. There is a case for complementing safe(r)-by-design studies by investigating the impact of the modifications studied on CuO nanoparticle functionality.

Keywords: CuO nanoparticles; safe(r)-by-design; coating; capping; doping; hazard; safety; functionality

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1. Introduction

Maynard et al. [1] called safe-by-design 'a grand challenge of safe nanotechnology'. In this journal, Martins and Kczarewska [2], discussing green nanotechnology, noted the importance of safer-by-design approaches as objects for future research. Reviews suggest that most of the research regarding safe(r)-by-design nanomaterials is in the field of nanomedicine, where the focus is on safety for humans in the use stage [3–5]. As to nanoparticles that can be applied outside the field of nanomedicine, there is now a substantial amount of research regarding safe(r)-by-design efforts based on modifications of CuO nanoparticles, which will be reviewed in Section 2.

CuO nanoparticles are used as biocides, for instance in wood preservation and antifouling, and presumably also in agricultural fungicides [6–10]. The proposed applications of CuO nanoparticles regard catalysts [11–13], sensing [14–16], solar stills [17], solar collectors [18,19] and additives in diesel fuels [20].

CuO nanoparticles are traditionally generated using methods from physics and inorganic chemistry. Approaches to synthesis include electrochemistry, sonochemistry, mechanochemistry and solvothermal and hydrothermal methods [15]. Nanoparticles generated by such methods will be considered here. It is possible to synthesize specific nanostructures, such as CuO nanorods, belts, fibers and flowers, but these will not be discussed. Recently, there has been an upsurge in the laboratory-scale biosynthetic generation of CuO nanoparticles, especially using plant extracts [21]. Such particles will be briefly referred to below.

Hazards of CuO nanoparticles apply to their production, processing, use and waste stages. In a variety of organisms, including invertebrates, plants and mammalian species, hazard of such CuO nanoparticles have been linked to the release of Cu ions and the pro-oxidant activity associated with the induced generation of reactive oxygen species (ROS) [22–31]. It may be noted, though, that Nations et al. [6] have found that exposure of the tadpole *Xenopus laevis* to low CuO nanoparticle concentrations positively affected

growth and metamorphosis, whereas, at higher concentrations, the impact on development was negative. The mechanism underlying this biphasic impact has not been clarified, but it has been reported that CuO nanoparticles may have an antioxidant effect by scavenging free radicals [32]. It has furthermore been documented by Ge et al. [33] and Podder et al. [34] that, dependent on morphology and concentration, several other metal oxide nanoparticles have an antioxidant effect, in which the scavenging of free radicals and the mimicking of antioxidant enzymes may be involved. Jiang et al. [35] studied manganese oxide nanoparticles that were predominantly antioxidant at low concentrations and predominantly pro-oxidant at higher concentrations. It may be that, similar to the manganese oxide nanoparticles studied by Jiang et al. [35], CuO nanoparticles may have a predominantly antioxidant effect at low nanoparticle concentrations. In the case of biosynthesized CuO nanoparticles, biogenic compounds with antioxidant activity might be present in the nanoparticles, enhancing the overall antioxidant activity of CuO nanoparticles [36,37]. An antioxidant effect is relevant to the hazard of metal oxide nanoparticles, e.g., [33].

One safe-by-design option for nanoparticles that prevents exposure during their use, is their irreversible binding to large inorganic substrates, e.g., [38]. This option may be considered for CuO nanoparticles in terms of their application in sensors and regarding a part of their proposed applications in catalysis. When irreversible binding to large inorganic substrates is at variance with nanoparticle functionality, the modification of CuO nanoparticles may be considered.

In two cases it has been claimed that modifications of Cu nanoparticles confer safety-by-design. Naatz et al. [39] studied CuO nanoparticles doped with Fe. The rationale behind this was that Fe-doping should decrease the dissolution of Cu ions which were held to be responsible for cytotoxicity. Such a decrease in metal ion dissolution was shown by Naatz et al. [39] in several media. Naatz et al. [39] furthermore tested Fe-doped and non-doped CuO nanoparticles as to their cytotoxicity in the human cell lines BEAS-2B and THP-1, and regarding their hatching inhibition of zebrafish embryos. Fe-doping was found to be linked to reduced cytotoxicity and reduced inhibition of hatching. Naatz et al. [39] concluded that their study demonstrated the safe use of (6–10%) Fe-doped CuO nanoparticles in the environment. Feng et al. [40] focused on the generation of reactive oxygen species (ROS) induced by Mn_3O_4 nanoparticles and in their conclusions generalized their findings to all metal oxide nanoparticles. Feng et al. [40] have shown that doping with about 5 (molar)% Zn is linked to a substantial reduction in ROS generation compared with non-doped Mn_3O_4 nanoparticles in exposed BEAS-2B cells. They concluded that the way doping by Zn shifts the Fermi energy edge far away from the valence band energy edge, to reduce pro-oxidant activity, becomes a feasible safe-by-design approach to achieve safe Mn_3O_4 nanoparticles, and more in general safe metal oxide nanoparticles. This would include CuO nanoparticles.

In the next two sections, studies regarding safe(r)-by-design efforts based on the modification of CuO nanoparticles will be reviewed. The central question asked is whether these efforts have led to safe functional CuO nanoparticles, cf. Figure 1.

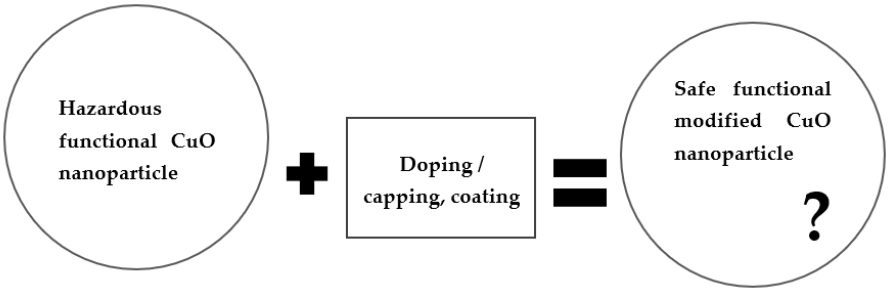

Figure 1. The central question: do doping or coating lead to safe functional Cu nanoparticles?

The focus will be on two matters. The fist regards the question of whether nanoparticle modifications have been be proven safe by the available studies. Safe is defined here as

posing no risk. Risk is the chance that negative impacts will occur. This is the subject of Section 2. The second matter, discussed in Section 3, is the compatibility of the modifications studied with the functionality of CuO nanoparticles. Section 4 summarizes the conclusions of this paper.

2. Safe(r)-By-Design CuO Nanoparticles

Safe(r)-by-design modifications of CuO nanoparticles target the release of Cu ions and/or the generation of reactive oxygen species (ROS) [39–47]. Two strategies can be found in safe-by-design studies. One safe-by-design strategy regarding CuO nanoparticles is based on coating or capping (surface modification), often with organic substances. Another safe-by-design strategy for CuO nanoparticles is based on doping. Both strategies will be considered here: surface modification by coating or capping in Section 2.1, and doping in Section 2.2. The focus will be on the impact of doping and coating on hazard. Toxicity will be used as a proxy for hazard. The matter of whether these studies addressed the impact of safe-by-design modifications on an antioxidant effect of CuO nanoparticles will also be addressed. Section 2.3 will raise the question as to whether the modified CuO nanoparticles discussed in Sections 2.1 and 2.2 are proven to be safe.

2.1. Surface Modification by Coating or Capping

The rationale for the surface modification of CuO nanoparticles by coating or capping is that the coating or capping may act as a scavenger for copper ions and reactive oxygen species [46–48]. It may be noted, though, that coating or capping may also increase nanoparticle hazard mechanisms [23]. An example thereof is the substantial increase in CuO nanoparticle toxicity to the green alga *Chlamydomonas reinhardtii* and the aquatic macrophyte *Lemna gibba* by coating CuO nanoparticles with styrene-butylacrylate co-polymer [23]. Perreault et al. [23] have suggested that this increase in toxicity is linked to changing nanoparticle interactions with cells and toxicity mechanisms.

In a safe-by-design study by Cai at al. [47] CuO nanoparticles were coated with citrate, polyvinylpyrrolidone (PVP) and aminomethylphosphonate. Testing was for cytotoxicity in the (human) cell lines BEAS-2B and THP-1 and for inflammation of mouse lung tissue. The reduction in negative impacts by CuO nanoparticles was very limited when coating was with citrate. In the case of coating with PVP, the reduction in negative impact was moderate and in the case of phosphonate coating was relatively large, though not complete.

In a safe-by-design study, Fiandra et al. [45] studied the impact on A549 human lung epithelial cells and *Xenopus laevis* embryos of capping of CuO with polyethyleneimine (PEI) and polyethyleneglycol (PEG). They found that modifying the surface of CuO nanoparticles with PEG reduced hazard, but capping with PEI did not. As to the mechanism underlying reduced hazard, Fiandra et al. [45] found in the case of exposure to CuO nanoparticles capped with PEG, that the generation of reactive oxygen species in cells was reduced. The presence of Cu ions in lung cells was higher in the case of PEI-capped CuO nanoparticles than in the case of their PEG-coated counterparts. Hazard was not eliminated by capping with PEG. Extrapolation of the findings of Fiandra et al. [45] to humans and the different ways of intake by humans is subject to uncertainty [49–51] and the extrapolation to other organisms that can be exposed to CuO nanoparticles is beset by uncertainties [50,52].

In a safe-by-design study, Gosens et al. [46] studied the impact of CuO nanoparticles surface-modified with ascorbate and PEI on short-term pulmonary inflammation in rats. These surface modifications had been tested before as to their cytotoxicity in a mouse macrophage cell line [41]. In the latter study ascorbate-modified CuO particles scored best in reducing cytotoxicity. However, Gosens et al. [46] found no significant differences as to toxic effects and toxic potency in the lungs of rats between the two surface modifications. This underlines the uncertainty in extrapolating outcomes of tests in cell lines to organisms. Inhalation hazard to rats was not eliminated by capping.

There is a set of studies testing the hazard of CuO nanoparticles coated with polyethylene glycol, carboxylate and methylaminated compounds, if compared with the hazard of

pristine CuO nanoparticles, in a variety of biological settings [43,48,53–55]. These studies will be briefly presented below. Table 1 compares the hazard of CuO nanoparticles coated with polyethylene glycol (PEGylated CuO nanoparticles), with the hazard of pristine CuO nanoparticles.

Table 1. Hazard of PEGylated CuO nanoparticles compared with pristine CuO nanoparticles.

Study	Object of Test	Hazard of PEGylated CuO Nanoparticles Compared with the Hazard of Pristine Nanoparticles
Tatsi et al. [43]	Earthworms	Reduced
Conolly et al. [48]	Haemocytes and lysosomes of mussels	Increased
Gajda-Meissner et al. [53]	Daphnia magna	Increased
Kubo et al. [54]	THP-1 and HACA human cell lines	Reduced
Ilves et al. [55]	Lungs of mice	Reduced

Tatsi et al. [43] used CuO nanoparticles with polyethylene glycol, carboxylate and methylaminated compounds in 14 days toxicity tests with earthworms. In fresh soil, CuO nanoparticles with a carboxylate and methylaminated coating were more toxic than pristine CuO nanoparticles, whereas PEGylated CuO nanoparticles had the lowest toxicity. In aged soil, Cu nanoparticles that had a methylaminated organic coating were more toxic than pristine CuO nanoparticles, whereas carboxylated and PEGylated CuO nanoparticles had (similar) lower toxicities than pristine CuO nanoparticles. Using CuO nanoparticles with the same coatings as used by Tatsi et al. [43], Gajda-Meissner et al. [53] concluded that coated CuO nanoparticles were more toxic in acute tests with *Daphnia magna* than pristine CuO nanoparticles. Kubo et al. [54] found that coatings of CuO nanoparticles with PEG and carboxylate reduced the cytotoxicity in the human cell lines THP-1 and HACAT, and that a methylaminated organic coating increased cytotoxicity. Extrapolation of these tests to human organisms is subject to uncertainty [49–51]. Ilves et al. [55] did show that pristine, methylaminated- and carboxylate-coated CuO nanoparticles strongly exacerbated allergen-induced lung inflammation in mice, but that the exacerbation was much less in the case of PEGylated CuO nanoparticles. Conolly et al. [48] studied the effect on mussels (*Mytilus* spp.) of pristine CuO nanoparticles and CuO nanoparticles coated with the same organic substances as used by Tatsi et al. [43]. The focus was on gill cells, lysosomes and haemocytes. Genotoxicity affecting DNA in gill cells and haemocytes was found for both pristine and coated CuO nanoparticles. Based on acute toxicity to lysosomes and haemocytes, the hazard potential of PEG-coated CuO nanoparticles was found to be larger than for the pristine CuO nanoparticles. Chronic exposures suggested lower levels of oxidative stress associated with pristine CuO nanoparticles than with CuO nanoparticles that had carboxylate coatings.

Ribeiro et al. [42] found that in an acute toxicity test coating or capping with organic substances (citrate, ascorbate, PEI and polyvinylpyrrolidone (PVP)) of CuO nanoparticles increased the negative impact on earthworm coelomocytes compared with pristine CuO nanoparticles.

In a safer-by-design study, Mendes et al. [44] considered surface-modification of CuO nanoparticles with citrate, ascorbate, PEI and PVP. These modifications were tested in a mesocosm with six soil invertebrate species (consumers) during relatively long periods, up to 84 days [44]. In this test, overall hazard was reported to be reduced by PEI, but actually increased by citrate and ascorbate modifications, whereas PVP had hardly any effect. Responses differed between species, suggesting species-specific response mechanisms. Mendes et al. [44] stressed the importance of long-term testing to assess nanoparticle hazard and stated that multispecies testing increases the relevance to ecological hazard. Multigenerational tests would seem preferable because, as pointed out by Yu et al. [56]

and Gomes et al. [57], there is evidence for transgenerational epigenetic effects. Extrapolation of these findings to other organisms that may be exposed to surface-modified CuO nanoparticles in a variety of environments is beset by uncertainties [50,52,58].

In proving that CuO nanoparticles with coatings or cappings are safe or safer, the robustness of coatings or cappings under conditions encountered in their use stage and beyond should be considered [50]. None of the studies discussed here addressed the robustness of coatings or cappings.

In summary: In the studies discussed here, the negative impacts of CuO nanoparticles can be decreased, increased and remain unaffected by coating or capping with organic substances. The series of papers regarding CuO nanoparticles coated with polyethylene glycol, carboxylate and methylaminated compounds ([43,48,53–55] did show that, for a specific coating, toxicities can differ substantially across species and components thereof. As indicated in Table 1, PEGylated CuO nanoparticles did in several cases show a lower toxicity than pristine CuO nanoparticles [43,54,55] but not in studies with *Daphnia magna* [53] and mussel lysosomes and haemocytes [48]. Tatsi et al. [43] also found that relative toxicities may differ in different environments (fresh and aged soil). This underlines that in extrapolations to all organisms of findings showing a decrease in the negative impacts for specific organisms, parts thereof and derived cell lines are beset by uncertainties. None of the studies discussed here showed the elimination of CuO nanoparticle hazard by coating or capping. Furthermore, none of these studies addressed the impact of safe-by-design modifications on an antioxidant effect of CuO nanoparticles, though changes in antioxidant effects can be relevant to safety [33].

2.2. Doping

In the Introduction it was noted that two studies [39,40] claimed that safety-by-design was achieved by doping. Table 2 summarizes the characteristics of CuO nanoparticles contributing to hazard that these studies addressed and their findings regarding these characteristics as impacted by doping.

Table 2. Characteristics of CuO nanoparticles that can contribute to hazard addressed by Naatz et al. [39] and Feng et al. [40] and their findings regarding these characteristics as impacted by doping.

Characteristic of Nanoparticle That Can Contribute to Hazard	Was This Addressed by Naatz et al. [39]? If So, What Impact of Doping Was Found?	Was This Addressed by Feng et al. [40]? If So, What Impact of Doping Was Found?
Release of metal ions	Yes, reduction of copper ion release was found.	No.
Generation of reactive oxygens species (ROS)	No	Yes, a reduced generation of ROS was found

As pointed out in the Introduction, Naatz et al. [39] studied the hatching inhibition of zebrafish embryos by Fe-doped CuO nanoparticles and found reduced inhibition of hatching, if compared with pristine CuO nanoparticles. Naatz et al. [39] also studied the effect of Fe-doped CuO nanoparticles on cytotoxicity in BEAS-2B and THP-1 (human) cell lines. In addition, Joshi et al. [59] studied exposure of (human) C6 glioma cell lines to Fe-doped and non-doped CuO nanoparticles. Both Naatz et al. [39] and Joshi et al. [59] found CuO nanoparticles were reduced by Fe-doping. As Joshi et al. [59] did show that the generation of reactive oxygen species (and its associated hazard) was to be unaffected by Fe-doping, whereas the release of Cu ions from CuO nanoparticles was slowed, reduced cytotoxicity was ascribed to the latter effect. Pugazhandi et al. [60] tested the impact of CuO nanoparticles doped with 3.6% Fe against three microbial species (two bacteria and one yeast). A substantial antimicrobial activity was found. The experiments presented by Naatz et al. [39], Pugazhandi et al. [60] and Joshi et al. [59] did not show that CuO nanoparticle hazard was eliminated by doping with Fe. Taking into account the uncertainties besetting extrapolation [49–52,58], these studies did not demonstrate that Fe-doped CuO nanoparticles can be safely used in the environment.

The induced generation of ROS by Mn_3O_4 nanoparticles as tested by Feng et al. [40] was not eliminated by Zn doping. The aim of the doping experiments performed by Feng et al. [40] has been to reduce the generation of ROS by keeping conduction band energy out of the biological redox potential range and having the edge of the Fermi energy (which dominates charge transfer) far away from the valence band energy edge. Feng et al. [40] were successful as to the latter but not regarding the former. As the conduction band of CuO nanoparticles has been reported in the same range as biological redox potentials [61], it would seem that the doping strategy used by Feng et al. [40] is also unlikely to eliminate the generation of ROS induced by doped CuO nanoparticles. Feng et al. [40] did not address the impact of Zn-doping on the release of metal ions from Mn_3O_4 nanoparticles, as they stated that these nanoparticles are insoluble. Insolubility, however, does not apply to CuO nanoparticles. In view of research presented by Ivask et al. [22], Naatz et al. [39] and Joshi et al. [59], the release of Cu ions from CuO nanoparticles in biologically relevant settings is well established. It might also be pointed out that Katsnelson et al. [62] and Illarionova et al. [63] have presented evidence for the release of Mn ions from Mn_3O_4 nanoparticles in organisms and cell lines. Finally, the extrapolation of the experiments performed by Feng et al. [40], regarding the cytotoxicity Zn-doped CuO nanoparticles to cell lines, to all organisms that can be exposed to CuO nanoparticles, is beset by uncertainties [49–52,58]. The experiments presented by Feng et al. [40] did not show that metal oxide nanoparticle hazard was eliminated by doping with Zn. The impact of doping with Zn on an antioxidant effect of metal oxide nanoparticles was not addressed by Feng et al. [40].

2.3. Are the Modified CuO Nanoparticles Discussed in This Section Safe?

None of the studies previously discussed in this section provided evidence for the elimination of hazard by safe(r)-by-design doped, coated or capped CuO nanoparticles. Still, one might argue that such elimination is not necessary for the absence of risk, as there may be exposure levels that do not give rise to negative impacts (no-negative effect levels) and exposure may remain below these levels. However, there is as yet no proof that this actually applies. Such proof is also complex. No-negative effect levels for modified CuO nanoparticles have not as yet been established. Their establishment is likely to be difficult, as Mendes et al. [44] have shown that there are substantial differences in the response to coated nanoparticles between species, and it is also known that the toxicity of Cu ions (central to the safety claim of Naatz et al. [39], shows large differences between species, between varieties and even between individuals [64–66]. Furthermore, as pointed out above, there are currently no data about the robustness of CuO nanoparticle coatings or cappings in the real world. In the real world, no-negative effect levels in practice depend on the presence of other substances. There may be co-exposure to other nanoparticles, e.g., to ZnO nanoparticles, which may give rise to strong interactions [67]. Furthermore, background-exposure data regarding other substances that induce the generation of ROS (central to the safety claim of Feng et al. [40]) and can release Cu ions are needed to establish no-negative effect levels for modified CuO nanoparticles in the real world. Such exposure data are currently patchy at best. Finally, realistic fate and exposure studies are needed to show that actual exposure remains below no-negative effect levels. Such studies are currently lacking. It can be concluded that the safe(r)-by-design studies regarding the modified doped, coated or capped CuO nanoparticles discussed here do not prove that these modified nanoparticles are indeed safe. Providing such proof does not seem feasible in the near future, due to its complexity and the present lack of data.

3. Safe(r)-By-Design and Functionality

Tavernaro et al. [68] have pointed out that safe(r)-by-design modifications may impact functionality. This is highly relevant to the use of CuO nanoparticles as biocides. The biocidal properties of Cu nanoparticles have been shown to involve the induce generation

of reactive oxygen species and the release of Cu ions [69–75], and these are the properties targeted by safe(r)-by-design modifications as discussed in Sections 2.1 and 2.2.

Only one of the safe(r)-by-design studies discussed here addressed the impact of the safe(r)-by-design modifications on the biocidal functionality of CuO nanoparticles. Kubo et al. [54] found that coatings of CuO with PEG and carboxylate reduced the cytotoxicity in the human cell lines THP1 and HACAT and improved the ratio of activity against *Escherichia coli* strain MG1655 versus human cell line cytotoxicity, when compared with pristine CuO nanoparticles. The significance of the results obtained by Kubo et al. [54] would seem to be limited. *Escherichia coli* strain MG1655 is not a known pathogen. Extrapolation of the cytotoxicity tests performed by Kubo et al. [54] to the impact on human organisms is subject to uncertainty [49–51]. Furthermore, extrapolations to other organisms are problematic as tests with earthworms [43], *Daphnia magna* [53] and mussels [48] suggested that coatings with carboxylates and PEG might also increase toxicity. Other studies regarding the impact of coating or capping CuO nanoparticles with organic compounds on biocidal activity have shown variable outcomes, which may be dependent on differences in interactions with cells and impacts on toxicity mechanisms [23]. Padmavathi et al. [74] found that capping CuO nanoparticles with cetyl trimethyl ammonium bromide reduced the antibacterial activity against *Staphylococcus lentus*. Sohail et al. [76] did show that the coating of biosynthetically produced Cu nanoparticles coated with polyamine increased the antifungal effect against *Aspergillus parasiticus*.

The proposed applications of CuO nanoparticles may also have functionalities that might be impacted by the safe(r)-by-design modifications considered here. The creation of electron holes which underlies sensing responses [16] might, e.g., be affected by shifting the edge of the Fermi energy (which dominates charge transfer) far away from the valence band energy edge, which is instrumental in hazard reduction by doping studied by Feng et al. [40]. As to the proposed application of CuO nanoparticles as catalysts, it may be noted that adsorption of reactants to CuO nanoparticles is important in catalytic activity [11,77]. This property might be impacted by coating or capping. As shown by Wang et al. [78] electron transfer can be implicated in the catalytic activity of CuO nanoparticles. It seems plausible that doping with Fe and Zn and coating or capping might affect such electron transfer.

The CuO functionalities' high thermal conductivity and absorbing solar radiation can be exploited in solar stills [17]. As the doping of CuO nanoparticles may, by changing the bandgap, impact the absorption of solar radiation [79], the functionality of doped CuO nanoparticles for use in solar stills may be affected. Furthermore, thermal conductivity may be negatively affected by doping by a metal [80], which may affect functionality in solar stills and collectors. As to the application of CuO particles as fuel additives, coating or capping with organic substances to improve safety is not a good option as organic substances will be degraded during combustion. Bitire et al. [20] suggested that the reduction of NO_x emissions by CuO nanoparticles in diesel combustion was linked to improved heat transfer, which, as pointed out above, might be affected by doping.

In view of the forgoing, there is a case to complement studies regarding safe-by-design modifications of CuO nanoparticles with studies regarding the implications thereof for functionality.

4. Conclusions

None of the studies considered here provided evidence for the elimination of hazard by the safe(r)-by-design doping, coating or capping of CuO nanoparticles. No study addressed the impact of these safe(r)-by-design modifications on an antioxidant effect of CuO nanoparticles, though changes in antioxidant effects can be relevant to safety. None of the studies regarding coatings or cappings addressed the robustness thereof. Nor has it been proven that levels of exposure to the modified nanoparticles discussed here remain below real world no-negative effect levels. Thus, the studies discussed here did not show that the CuO nanoparticle modifications they considered are safe (no risk). By targeting

the release of Cu ions and the generation of reactive oxygen species by CuO nanoparticles, safe(r)-by-design studies target properties that underly the biocidal functionality of CuO nanoparticles. Functionality of CuO nanoparticles in other applications, e.g., in catalysis, solar stills and fuels, may also be impacted. Against this background there is a case for complementing safe(r)-by-design studies by investigating the impact of the modifications studied on CuO nanoparticle functionality. All in all, it has not been proven that the modified CuO nanoparticles discussed in this review are safe and functional.

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