Assessment of the biological effect of metal ions and their complexes using *Allium cepa* and *Artemia salina* assays: a possible environmental implementation of biological inorganic chemistry

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Abstract
The pollution of aquatic ecosystems due to the elevated concentration of a variety of contaminants, such as metal ions, poses a threat to humankind, as these ecosystems are in high relevance with human activities and survivability. The exposure in heavy metal ions is responsible for many severe chronic and pathogenic diseases and some types of cancer as well. Metal ions of the groups 11 (Cu, Ag, Au), 12 (Zn, Cd, Hg), 14 (Sn, Pb) and 15 (Sb, Bi) highly interfere with proteins leading to DNA damage and oxidative stress. While, the detection of these contaminants is mainly based on physicochemical analysis, the chemical determination, however, is deemed ineffective in some cases because of their complex nature. The development of biological models for the evaluation of the presence of metal ions is an attractive solution, which provides more insights regarding their effects. The present work critically reviews the reports published regarding the toxicity assessment of heavy metal ions through *Allium cepa* and *Artemia salina* assays. The in vivo toxicity of the agents is not only dose depended, but it is also strongly affected by their ligand type. However, there is no comprehensive study which compares the biological effect of chemical agents against *Allium cepa* and *Artemia salina*. Reports that include metal ions and complexes interaction with either *Allium cepa* or *Artemia salina* bio-indicators are included in the review.

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Abbreviations

| Abbreviation | Full Form |
|--------------|-----------|
| %MIA | % Mitotic Index Alteration |
| 2,3BTSTCH2 | Thiophene-2,3-dicarboxaldehyde bis(thiosemicarbazone) |
| AdNH2 | Amantadine |
| aphaOEt | 2-Acetylpyridine ethyl hydrazinocacetate hydrochloride |
| bipy | 2,2-Bipyridine |
| BzimetTSCH | 1-(1H-Benzimidazol-2-yl)ethan-1-one thiosemicarbazone |
| CA | Chromosomal abnormalities |
| CAH | Cholic acid |
| CIPH | Ciprofloxacin |
| dapha(OEt)2 | 2,6-Diacetylpyridine ethyl hydrazinocacetate hydrochloride |
| FAO | Food and Agriculture Organization of the United Nations |
| GlyH | Glycine |
| H2Am4DH | 2-Pyridineformamide thiosemicarbazone |
| H2Am4Et | N(4)-Ethyl-2-pyridineformamide thiosemicarbazone |
| H2Am4Me | N(4)-Methyl-2-pyridineformamide thiosemicarbazone |
| H2Am4P | N(4)-Phenyl-2-pyridineformamide thiosemicarbazone |
| H2mna | 2-Mercapto-nicotinic acid |
| INH | Isoniazid |
| LC50 | Lethal Concentration (mM) that eliminates the 50% of the nauplii |
| LD50 | Lethal Dose (mg/mL) that eliminates the 50% of the nauplii |
| Me2DTC | Dimethyldithiocarbamate |
| MI | Mitotic index |
| MMI | 2-Mercapto-1-methyl-imidazole |
| MN | Micronucleus |
| NA | Nuclear abnormalities |
| NCS | N-Chlorosuccinimide |
| NMP | N-Methyl pyrrolidone |
| ORLE | Extract from oregano leaves |
| PenH | Penicillin G |
| phen | 1,10-Phenanthroline |
| salH2 | Salicylic acid |
| SCP | Sulfachloropyridazine |
| SDM | Sulfadimetoxine |
| SMX | Sulfamoxole |
| TPP | Triphenylphosphate |
| valp | Valproic acid |
| WHO | World Health Organization |
**Introduction**

Although some metal trace elements are essential for life, playing an important role e.g., in transportation and signaling between cells, however, metal ions, such as Cd, Pb, As, Cr and Hg, is considered as hazardous to the health even at low concentration [1, 2]. The toxicity of heavy metals is emerged from their ability to inhibit enzymes, cause oxidative stress and suppress the antioxidant mechanisms, leading to DNA damage [2]. Moreover, the heavy metals impair the function of the nervous system causing Alzheimer’s disease and neuronal disorders [1]. Chronic inflammatory diseases and cancer are some of the most well-known pathogenic effects of heavy metals in humans [2]. Ni and its compounds may cause respiratory cancer, inhalation disorders, dermatitis and reproductive problems [3]. Extended exposure to Ni leads to genotoxic and epigenetic changes, rendering Ni a possible carcinogenic agent [3]. Pb mainly induces oxidative stress and renin–angiotensin system stimulation [1]. It may disrupt the normal regulation of heart’s autonomic nerve, provoking many heart diseases, such as hypertension, coronary heart disease, stroke and peripheral arterial disease [1]. In addition, its presence has been linked with erythropoiesis and heme biosynthesis problems, anemia and some cancer types [1]. Cd is also carcinogenic and affects kidneys, bone metabolism and reproductive and endocrine systems [1]. Cd’s ability to activate calmodulin results in muscle dysfunctions and diseases like Itai-Itai disease and renal tubular dysfunction [1]. Moreover, Hg binds to enzymes and proteins, causing pneumonitis, non-cardiogenic pulmonary edema and acute respiratory distress [1]. It is considered to be an extremely hazardous element, because of its ability to cross the blood–brain barrier [1]. Methylmercury is a known neurotoxin [1]. Minamata disease is one of the diseases caused by Hg [1].

Humans are exposed to heavy metals mainly through food, cosmetic products, automobiles, radiation and effluents from a variety of industries [4]. The effort to restrict the exposure, the intake and the absorption of heavy metals by humans led the World Health Organization (WHO), Food and Agriculture Organization of the United Nations (FAO) and European Union (EU) to the establishment of guidelines regarding their concentration in food [5], drinking water [6] and water for irrigation purposes [7]. Especially the contamination of the environment due to heavy metals is a severe problem with which humankind has to deal [8]. Thus, the monitoring and the assessment of heavy metals in ecosystems is considered essential to manage the pollution they cause [8]. Since complexes formation of metal ions with ligands change the metal adsorption, bioavailability, bioaccumulation, toxicity behavior, etc. of free metal ions, the evaluation of metal complexes in ecosystems is also a research, technological and financial issue of great importance [9].

The most common way to detect the presence of heavy metals is the use of physicochemical analysis of water or sediment samples [10]. However, due to the complex nature of environmental wastes, a short-term toxicity based bioassays may increase the efficiency of the chemical analytical techniques [10, 11]. Biological systems are important indicators of aquatic pollution in combination with the pre-mentioned characterizations [10]. Therefore, biological assays, such as *Allium cepa* and *Artemia salina* assays, were already used for detecting the genotoxicity [12, 13]. *Allium cepa* assay has been standardized by the United Nations Environment Program and the Environmental Protection Agency’s (EPA) international programs as bio-indicator for the risk assessment of heavy metals ions contamination and the determination of their genotoxicity [14, 15]. *A. cepa* assay enables the detection of different genetic endpoints for the cytotoxic, genotoxic, clastogenic and aneugenic effects of toxic substances [12]. The Mitotic index (MI), chromosomal abnormalities (CA), nuclear abnormalities (NA) frequencies and micronucleus (MN) can be used as indicators to assess the cytotoxicity of several agents [12]. *Artemia salina* is a zooplanktonic crustacean [13] and it can be found in a variety of seawater systems [13]. *A. salina* interacts with the aquatic environment and faces high risk exposure to contaminants [13]. For the toxicological evaluation, endpoints can be used, such as hatching, mortality, swimming, morphology and biomarkers [13]. Moreover, nauplii of the brine shrimp have been considered a simple and suitable model system for acute toxicity tests [13].

Within this review, the reports on the assessment of the biological effect of metal ions and their complexes using the *Allium cepa* and *Artemia salina* assays are critically discussed. Reports that include metal ions and complexes interaction with either *Allium cepa* or *Artemia salina* bio-indicators are included in the review. Metal ions of the groups 11 (Cu, Ag, Au), 12 (Zn, Cd, Hg), 14 (Sn, Pb) and 15 (Sb, Bi), was selected during the literature search. Therefore, all works published on this subject were included to the best of our knowledge.

**Results and discussion**

**Allium cepa** assay

The need for in vivo sensitive tools for toxicity monitoring is increasing and experimental models, besides animals, are becoming popular. *A. cepa* exhibits many similarities with the mammalian test models [13]. The assay based on this plant is useful for the detection and the evaluation of the
effects or the presence of a contaminant, such as metal ions [13]. The influence of such contaminants on the MI and the DNA damage (CA, NA, MN) is estimated after the 24 h or 48 h exposure of A. cepa roots in different concentrations of the contaminant [13].

This review examines the effects of heavy metal ions on the MI and the CA, which were observed in the onion cells. The MI% is defined as the ratio between the cells in a population undergoing mitosis to the cells not undergoing mitosis [16]. CAs emerge from the exposure to physical or chemical agents and are presented as changes in chromosomal structure or in the total number of chromosomes [17]. MN is arisen from the development of CA, and result from damages, not or wrongly repaired, in the parental cells [14]. More specifically, chromosomal loses and fragments, which are not included in the main nucleus, form a smaller structure, which is called micronucleus [14]. CAs are chromosomal bridges, chromosomal loss, stickiness, c-mitosis, etc. [17]. The first two belongs to clastogenic aberrations, along with chromosomal breaks, while the others are included to physiological aberrations [18]. Stickiness is emerged from the high condensation of chromosomes or the depolymerization of DNA and its outcome is cell death in most cases [18]. C-mitosis is the scattering of the chromosomes all over the cell because of the prevention of the formation of spindle fibers due to colchicines [18]. Vagrant and laggard/lagging chromosomes are also physiological aberrations [18]. The first one describes the movement of a chromosome ahead of its group, leading to unequal separation, while the second refers to the chromosomes that fail to attach to the spindle fiber [18]. Another chromosomal aberration is called clumping and reports the appearance of a cluster of chromosomes in different phases of cell cycle [19]. Chromosomal adherence is another term for approximately the same effect, namely the presence of attached chromosomes [14]. Finally, tripolar mitosis describes the separation of chromosomes in three poles due to the presence of three strands of a division spindle [20]. Some common CA types are presented in Fig. 1.

To compare the MI% values of the A. cepa root cells after their exposure to different metal complexes or salts, we introduce a new term the % Mitotic Index Alteration upon their incubation in a particular concentration of the agent (% MIA(C)). This is necessity due to the control samples quality diversity used as well as the variety of A. cepa bulb types. Thus, % MIA(C) corresponds to a specific MI % control value at a specific concentration (C).

\[
\% MIA(C) = \frac{100 \times MI(C)_{\text{sample}}}{MI(C)_{\text{control}}}
\]

% MIA(C) indicates the percentage of the cells which undergo mitosis in a specific concentration, in respect to the corresponding percentage in the control sample. So, a reduction in % MIA(C) reflects the reduction of the number of cells undergoing mitosis and, consequently, the decrease of

Fig. 1 CA observed in A. cepa root cells. A Chromosomal loss or fragment in anaphase, B Chromosomal loss or fragment in metaphase, C Chromosomal loss or fragment in prophase, D Chromosomal bridge in anaphase, E C-mitosis and F Micronucleus.

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cell viability. According to ISO 10993-5:2009, a substance is considered as non-toxic, if it promotes the death of < 30% of the cells (viability ≥ 70%) [21, 22]. We extend here the assumption that if an agent introduces % MIA(C) ≥ 70%, then it is considered as a non-toxic as well. It is pointed out that the samples numbering shows their ingredients, in a particular concentration.

**Group 10 metals (Ni, Pd, Pt) complexes**

**Platinum:** Samples of platinum(II) compounds with the thiosemicarbazone 1-(1H-Benzimidazol-2-yl)ethan-1-one thiosemicarbazone (BzimetTSC), formulae [Pt(BzimetTSC)(Cl)2H2O (1) and [Pt(BzimetTSC)(TPP)Cl]H2O-MeCN (2) (TPP = triphenylphosphine) were examined for their in vivo toxicity at 3 (1.1 and 2.1), 30 (1.2 and 2.2) and 300 (1.3 and 2.3) μM (Table 1). The range of % MIA values lies between 54.0 and 73.0% for the samples 1.1–1.3, while in the case of the samples 2.1–2.3, is between 73.0 and 64.0% (Table 1). In the case of the samples 2.2–2.3, the CA are increased in contrast to control [23].

The in vivo toxicity of tetrapyridylporphyrin containing four chloro(2,2′-bipyridine)platinum(II) complex (3-H2TPt-PyP) (3.1–3.4) attached at the meta position of the peripheral pyridine ligand was tested at 0.6–5.5 μM (Table 1). The sample shows no in vivo toxicity since the %MIA is almost 100 at the highest concentration (3.4), which is in consistent with the % root length [24].

*Allium cepa* bulbs were exposed for 24 h to aqueous solutions of cisplatin (4.1–4.4) and carboplatin (5.1–5.5) (Table 1). The % MIA values showed that cisplatin was toxic at the concentration of 1 and 5 μM, whereas carboplatin was not toxic in the tested concentrations [25].

**Group 11 metals (Cu, Ag, Au) complexes**

**Copper:** *Allium cepa* bulbs were incubated with samples of nano-silica Schiff-base Cu(II) (Silica-NMP-Cu, NMP = N-methyl pyrrolidone) (1.50 (6.1), 3.00 (6.2) and 6.00 (6.3) mg/L) (Table 1). The samples numbering corresponds to their ingredients, in a particular concentration. For example, the code 6.1 refers to the sample of Silica-NMP-Cu at the concentration of 1.50 mg/L. The % MIA of the Cu(II) was in the range of 90.4–96.8%, suggesting that its in vivo genotoxicity is low (Table 1). The percentage of CAs was similarly to those observed in lower concentrations. Chromosome adherences or chromosome losses were the most common types of CAs [29].

**Silver:** *Allium cepa* bulbs were incubated with [Ag3(Gly)2NO3]6 (GlyH = glycine) (AGGLY) at the concentrations range of 24–98 μM (7.1–7.3) (Table 1) [23]. The % MIA values varied from 68 (7.3) to 92 (7.2) %. The CA was 0.5% for 7.1, 0.33% for 7.2 and 0.41% for 7.3. These values suggest a low in vivo toxic activity (ISO 10993–5:2009) of [Ag3(Gly)2NO3]6 [27].

The combination of the antibiotic ciprofloxacin (CIPH) with silver(I) ions resulted to the [[Ag(CIPH)2]NO3·0.75MeOH·1.2H2O (CIPAG)] [16]. The silver(I) compound was assessed for its in vivo toxicity through *A. cepa* test in different concentrations (0.3 (8.1), 3 (8.2) and 30 (8.3) μM). The %MIA values were 90 (8.3)–99% (8.1) (Table 1). The CA values were 0.0–1.0% (8.3–8.1) (Table 1). Thus, neither %MIA nor CA are affected by the presence of the silver compound [16].

The in vivo toxicity of the silver(I) compound of formula [[Ag6(μ2-Hmna)(μ2-mna)F3−·(Et3NH)+12·(DMSO)2·(H2O)} (H2mna = 2-mercapto-nicotinic acid) (AGMNA) was tested in the concentrations of 3 (9.1), 30 (9.2) and 300 (9.3) μM (Table 1) [28]. The cell division rate of *A. cepa* root cells was not affected by the presence of AGMNA since the range of % MIA lies between 82 and 94%. The same trend was followed by CAs, (0.4% (9.2) to 0.8% (9.3)). Therefore, AGMNA has no in vivo toxic or mutagenic effects according to ISO 10993-5:2009 [21, 22].

The in vivo toxicity of [Ag(salH)]2 (salH2 = salicylic acid) (AGSAL) (3 (10.1), 30 (10.2) and 300 (10.3) μM) is tested by *A. cepa* assay (Table 1) [29]. No variation in % MIA values was observed at the concentrations up to 30 μM (Table 1). However, when *Allium cepa* were incubated with AGSAL at the concentration of 300 μM, the % MIA values reduced to the 34%, while the CAs doubled in respect to those observed in lower concentrations. Chromosome adherences or chromosome losses were the most common types of CAs [29].

Samples of two silver(I) compounds [AgBr(μ2-S-MMI) (TPP)]2 (11.1–11.3) and [AgCl(TPP)2(MMI)] (12.1–12.3) (TPP = triphenylphosphine, MMI = 2-mercapto-1-methyl-imidazole or methimazole) were evaluated through *A. cepa* assay (Table 1) [30]. No effect in % MIA was observed upon their incubation with 11.1–11.3 and 12.1–12.3. The absence of variations in the CA values indicates the absence of in vivo toxic behavior [30].

The samples of the silver(I) compounds [Ag(SCP)] (13.1–13.5) and [Ag3(Ag(SCN)3(SCP))·H2O] (SCP = Sulfa-chloroppyridazine) (14.1–14.5) were tested with *A. cepa* assay (Table 1). In vivo toxicity was detected considering both % MIA and root lengths, after their exposure to silver complexes solutions for 24 h (Table 1) [31]. Thus, the % MIA in the case of 13.2–13.5 lies between 42 and 68%. This is consistent with the high percentage reduction of the root length (20–60%), toward the corresponding of the control sample. However, the presence of SCN− anion in the coordination sphere increases the in vivo toxic limit at the concentration of 1.4 mM (14.5), with the % MIA value to be 33% for this concentration [31].

Similarly, the samples of compounds Ag(SDM) (15.1–15.5), Ag3SDM(SCN)2·H2O (16.1–16.5) and Ag5(SDM)2·phen ·H2O (17.1–17.5)
| Code | Molecular formula | Molecular weight (g/mol) | C (μM) | MI (%) | MIA% | CA (%) | Refs. |
|------|------------------|--------------------------|--------|--------|------|-------|-------|
| 1.1  | [Pt(BzimetTSCH)Cl]·2H2O | 498.86 | 3   | 4.7   | 70% | 0.9  | [23] |
| 1.2  | [Pt(BzimetTSCH)Cl]·2H2O | 498.86 | 30  | 4.9   | 73% | 1.3  | [23] |
| 1.3  | [Pt(BzimetTSCH)Cl]·2H2O | 498.86 | 300 | 3.6   | 54% | 1.8  | [23] |
| 2.1  | [Pt(BzimetTSCH)(tpp)Cl2H2O·MeCN | 784.17 | 3   | 4.4   | 66% | 1.2  | [23] |
| 2.2  | [Pt(BzimetTSCH)(tpp)Cl2H2O·MeCN | 784.17 | 30  | 4.9   | 73% | 2.1  | [23] |
| 2.3  | [Pt(BzimetTSCH)(tpp)Cl2H2O·MeCN | 784.17 | 300 | 4.3   | 64% | 2.7  | [23] |
| 2.4  | ddH2O | | | 6.7   | 1.3  | | [23] |
| 3.1  | 3-H2TPtPyP | 2165.58 | 0.6 | 57.0* | 04% | | [24] |
| 3.2  | 3-H2TPtPyP | 1.1 | 54.0 | 98% | | | [24] |
| 3.3  | 3-H2TPtPyP | 2.2 | 56  | 102% | | | [24] |
| 3.4  | 3-H2TPtPyP | 5.5 | 56  | 102% | | | [24] |
| 3.5  | Control | | | 55 | | | [24] |
| 4.1  | [Pt(NH3)2Cl2] | 300.05 | 0.1 | 11 | 81% | | [25] |
| 4.2  | [Pt(NH3)2Cl2] | 300.05 | 0.5 | 10.5 | 78% | | [25] |
| 4.3  | [Pt(NH3)2Cl2] | 300.05 | 1 | 2.5 | 19% | | [25] |
| 4.4  | [Pt(NH3)2Cl2] | 300.05 | 5 | 1.4 | 10% | | [25] |
| 4.5  | Control cisplatin | | | 13.5 | | | [25] |
| 5.1  | Carboplatin | 371.25 | 0.5 | 19 | 136% | | [25] |
| 5.2  | Carboplatin | 371.25 | 1 | 15 | 107% | | [25] |
| 5.3  | Carboplatin | 371.25 | 10 | 12.5 | 89% | | [25] |
| 5.4  | Carboplatin | 371.25 | 50 | 14.5 | 104% | | [25] |
| 5.5  | Carboplatin | 371.25 | 100 | 13 | 93% | | [25] |
| 5.6  | Control carboplatin | | | 14 | | | [25] |
| 6.1  | Silica-NMP-Cu | 1.0 e2 | 0.9 | 96.8 | 0.05 | | [26] |
| 6.2  | Silica-NMP-Cu | 3.0 e2 | 0.9 | 93.6 | 0.06 | | [26] |
| 6.3  | Silica-NMP-Cu | 6.0 e2 | 0.9 | 90.4 | 0.06 | | [26] |
| 6.4  | ddH2O | | | 6.7 | 0.5 | | [26] |
| 7.1  | ([Ag3(Gly)2NO3]n) | 542.75 | 24 | 8.2 | 85% | 0.5 | [27] |
| 7.2  | ([Ag3(Gly)2NO3]n) | 542.75 | 49 | 8.9 | 92% | 0.3 | [27] |
| 7.3  | ([Ag3(Gly)2NO3]n) | 542.75 | 98 | 6.6 | 68% | 0.4 | [27] |
| 7.4  | ddH2O | | | 9.7 | | | [27] |
| 8.1  | ([Ag(CIPH)2]NO3·0.75MeOH·1.2H2O | 872.78 | 0.3 | 6.6 | 99% | 1 | [16] |
| 8.2  | ([Ag(CIPH)2]NO3·0.75MeOH·1.2H2O | 872.78 | 3 | 6.2 | 93% | 0.6 | [16] |
| 8.3  | ([Ag(CIPH)2]NO3·0.75MeOH·1.2H2O | 872.78 | 30 | 6 | 90% | 0 | [16] |
| 8.4  | ddH2O | | | 6.7 | 0.5 | | [16] |
| Code | Molecular formula | Molecular weight (g/mol) | C (µM) | MI (%) | MIA% | CA (%) | Refs. |
|------|------------------|--------------------------|--------|--------|------|--------|-------|
| 9.1  | {[Ag₆(μ₃-Hmna)₄(μ₃-mna)₂]²⁻·(Et₃NH)₂·(DMSO)₂·(H₂O)} | 1948.7 | 3 | 4.1 | 82% | 0.5 | [28] |
| 9.2  | {[Ag₆(μ₃-Hmna)₄(μ₃-mna)₂]²⁻·(Et₃NH)₂·(DMSO)₂·(H₂O)} | 1948.7 | 30 | 4.5 | 90% | 0.4 | [28] |
| 9.3  | {Ag₆(μ₃-Hmna)₄(μ₃-mna)₂}²⁻·(Et₃NH)₂·(DMSO)₂·(H₂O)} | 1948.7 | 300 | 4.7 | 94% | 0.8 | [28] |
| 9.4  | dH₂O | - | - | - | - | - | [28] |
| 10.1 | [Ag(saH)]₂ | 489.96 | 3 | 7.2 | 107% | 0.6 | [29] |
| 10.2 | [Ag(saH)]₂ | 489.96 | 30 | 6.7 | 100% | 0.3 | [29] |
| 10.3 | [Ag(saH)]₂ | 489.96 | 300 | 2.3 | 34% | 0.8 | [29] |
| 10.4 | dH₂O | - | - | - | 6.7 | 100% | 0.4 | [29] |
| 11.1 | [AgBr(μ₂-S-MMI)(TPP)]₂ | 1128.44 | 3 | 6.8 | 117% | 1.4 | [30] |
| 11.2 | [AgBr(μ₂-S-MMI)(TPP)]₂ | 1128.44 | 30 | 5.3 | 91% | 0.3 | [30] |
| 11.3 | [AgBr(μ₂-S-MMI)(TPP)]₂ | 1128.44 | 300 | 5.3 | 91% | 0.7 | [30] |
| 12.1 | [AgCl(TPP)₂(MMI)] | 782.04 | 3 | 4.8 | 83% | 1.1 | [30] |
| 12.2 | [AgCl(TPP)₂(MMI)] | 782.04 | 30 | 5.2 | 90% | 0.6 | [30] |
| 12.3 | [AgCl(TPP)₂(MMI)] | 782.04 | 300 | 5.5 | 95% | 1 | [30] |
| 12.4 | dH₂O | - | - | - | 5.8 | 1.1 | [30] |
| 13.1 | [Ag(SCP)] | 391.58 | 3.2 | 39.6 | 71% | | [31] |
| 13.2 | [Ag(SCP)] | 391.58 | 16 | 38 | 68% | | [31] |
| 13.3 | [Ag(SCP)] | 391.58 | 63.8 | 28.4 | 51% | | [31] |
| 13.4 | [Ag(SCP)] | 391.58 | 159.6 | 26 | 47% | | [31] |
| 13.5 | [Ag(SCP)] | 391.58 | 319.2 | 23.6 | 42% | | [31] |
| 13.6 | Control | [Ag(SCP)] | - | - | 55.6 | 100% | | [31] |
| 14.1 | (Ag₃[Ag(SCN)₃(SCP)]H₂O) | 907.41 | 1.4 | 37 | 101% | | [31] |
| 14.2 | (Ag₃[Ag(SCN)₃(SCP)]H₂O) | 907.41 | 6.9 | 47 | 129% | | [31] |
| 14.3 | (Ag₃[Ag(SCN)₃(SCP)]H₂O) | 907.41 | 27.6 | 35.9 | 98% | | [31] |
| 14.4 | (Ag₃[Ag(SCN)₃(SCP)]H₂O) | 907.41 | 68.9 | 27.8 | 76% | | [31] |
| 14.5 | (Ag₃[Ag(SCN)₃(SCP)]H₂O) | 907.41 | 137.8 | 12 | 33% | | [31] |
| 14.6 | Control | [Ag₃[Ag(SCN)₃(SCP)]H₂O) | - | - | 36.6 | 100% | | [31] |
| 15.1 | Ag(SDM) | 417.19 | 31 | - | 176% | - | [32] |
| 15.2 | Ag(SDM) | 417.19 | 153 | - | 99% | - | [32] |
| 15.3 | Ag(SDM) | 417.19 | 306 | - | 100% | - | [32] |
| 15.4 | Ag(SDM) | 417.19 | 458 | - | 81% | - | [32] |
| 15.5 | Ag(SDM) | 417.19 | 611 | - | 103% | - | [32] |
| 16.1 | Ag₃(SDM)[SCN]₂·H₂O | 767.12 | 16.4 | 131% | - | [32] |
| 16.2 | Ag₃(SDM)[SCN]₂·H₂O | 767.12 | 82 | 118% | - | [32] |
| Code | Molecular formula | Molecular weight (g/mol) | C (μM) | MI (%) | MIA% | CA (%) | Refs. |
|------|-------------------|--------------------------|--------|--------|------|--------|-------|
| 16.3 | Ag₃SDM(SCN)₂·H₂O | 767.12                   | 164    | 126%   | –    | –      | [32]  |
| 16.4 | Ag₃SDM(SCN)₂·H₂O | 767.12                   | 246    | 74%    | –    | –      | [32]  |
| 16.5 | Ag₃SDM(SCN)₂·H₂O | 767.12                   | 328    | 120%   | –    | –      | [32]  |
| 16.6 | Control for [Ag(SDM)]₂Ag₃SDM(SCN)₂·H₂O | – | – | – | – | – | [32]  |
| 17.1 | Ag₂(SDM)₂·o-phen]·H₂O | 1032.61                 | 12.5   | 97%    | –    | –      | [32]  |
| 17.2 | Ag₂(SDM)₂·o-phen]·H₂O | 1032.61                 | 62.6   | 0%     | –    | –      | [32]  |
| 17.3 | Ag₂(SDM)₂·o-phen]·H₂O | 1032.61                 | 125    | 0%     | –    | –      | [32]  |
| 17.4 | Ag₂(SDM)₂·o-phen]·H₂O | 1032.61                 | 188    | 0%     | –    | –      | [32]  |
| 17.5 | Ag₂(SDM)₂·o-phen]·H₂O | 1032.61                 | 250    | 0%     | –    | –      | [32]  |
| 17.6 | Control for Ag₂(SDM)₂·o-phen]·H₂O | – | – | – | – | – | [32]  |
| 18.1 | [Ag₂(SMX)₂]·H₂O | 766.34                   | 1.6    | 37.8   | 78%  | –      | [33]  |
| 18.2 | [Ag₂(SMX)₂]·H₂O | 766.34                   | 8.2    | 37.7   | 77%  | –      | [33]  |
| 18.3 | [Ag₂(SMX)₂]·H₂O | 766.34                   | 32.6   | 36.2   | 74%  | –      | [33]  |
| 18.4 | [Ag₂(SMX)₂]·H₂O | 766.34                   | 81.2   | 28.4   | 58%  | –      | [33]  |
| 18.5 | [Ag₂(SMX)₂]·H₂O | 766.34                   | 326.2  | 17.2   | 35%  | –      | [33]  |
| 18.6 | Control [Ag₂(SMX)₂]·H₂O | – | – | – | – | – | [33]  |
| 19.1 | [Ag₄(SCN)₃(SMX)]·H₂O | 890.03                  | 1.3    | 45.6   | 98%  | –      | [33]  |
| 19.2 | [Ag₄(SCN)₃(SMX)]·H₂O | 890.03                  | 6.4    | 51.1   | 110% | –      | [33]  |
| 19.3 | [Ag₄(SCN)₃(SMX)]·H₂O | 890.03                  | 25.5   | 37.3   | 67%  | –      | [33]  |
| 19.4 | [Ag₄(SCN)₃(SMX)]·H₂O | 890.03                  | 63.8   | 31     | 41%  | –      | [33]  |
| 19.5 | [Ag₄(SCN)₃(SMX)]·H₂O | 890.03                  | 280.9  | 19     | 41%  | –      | [33]  |
| 19.6 | Control [Ag₄(SCN)₃(SMX)]·H₂O | – | – | – | – | – | [33]  |
| 20.1 | [Au(tpp)Cl] | 494.7                   | 3      | 6.7    | 102% | 0.3    | [34]  |
| 20.2 | [Au(tpp)Cl] | 494.7                   | 30     | 3.7    | 56%  | 0.3    | [34]  |
| 20.3 | [Au(tpp)Cl] | 494.7                   | 300    | 3.7    | 56%  | 1.5    | [34]  |
| 20.4 | ddH₂O | – | 6.6 | 22% | 0.6 | – | [34] |
| 21.1 | ZnO-NPs | 5*3 | 60 | 42% | – | – | [35] |
| 21.2 | ZnO-NPs | 50*3 | 31 | 22% | – | – | [35] |
| 21.3 | control | – | 144 | – | – | – | [35] |
| 22.1 | Zn(NO₃)₂ | 189.36                  | 0.77   | 110   | 183% | 0      | [36]  |
| 22.2 | Zn(NO₃)₂ | 189.36                  | 7.7    | 41    | 68%  | 2      | [36]  |
| 22.3 | Zn(NO₃)₂ | 189.36                  | 76.9   | 20    | 33%  | 2.3    | [36]  |
| 23.1 | Cd(NO₃)₂ | 236.42                  | 0.44   | 53    | 88%  | 0.8    | [36]  |
| 23.2 | Cd(NO₃)₂ | 236.42                  | 4.4    | 32    | 53%  | 1.6    | [36]  |
| Code | Molecular formula | Molecular weight (g/mol) | C (μM) | MI (%) | MIA% | CA (%) | Refs. |
|------|-------------------|--------------------------|--------|--------|-------|--------|-------|
| 23.3 | Cd(NO₃)₂          | 236.42                   | 44.4   | 16     | 27%   | 1.9    | [36]  |
| 23.4 | control           |                          | 62     |        |       |        | [36]  |
| 24.1 | CdCl₂             | 183.31                   | 50     | 39.2   | 41.7  | 74%    | 91%   | 5.9   | 2.9   | [37]  |
| 24.2 | CdCl₂             | 183.31                   | 80     | 49.9   | 49.8  | 94%    | 109%  | 4.7   | 4.5   | [37]  |
| 24.3 | CdCl₂             | 183.31                   | 100    | 35.7   | 44.2  | 67%    | 96%   | 20    | 2     | [37]  |
| 24.4 | dH₂O              |                          | -      | 53.2   | 45.9  | 100%   | 100%  | 0     | 0     | [37]  |
| 25.1 | PH₃Sn(CA)         | 757.5                    | 0.1    | 2.7    |        | 77%    | 0.6   | [38]  |
| 25.2 | PH₃Sn(CA)         | 757.5                    | 1      | 3.5    |        | 100%   | 2.8   | [38]  |
| 25.3 | PH₃Sn(CA)         | 757.5                    | 10     | 1.3    |        | 37%    | 2.5   | [38]  |
| 26.1 | n-BuSn(CA)        | 697.5                    | 0.1    | 4      |        | 114%   | 0.7   | [38]  |
| 26.2 | n-BuSn(CA)        | 697.5                    | 1      | 3.5    |        | 100%   | 1.7   | [38]  |
| 26.3 | n-BuSn(CA)        | 697.5                    | 10     | 2.2    |        | 63%    | 1.2   | [38]  |
| 27.1 | Ph₂Sn(CA)₂        | 1087.9                   | 0.1    | 2.8    |        | 80%    | 0.3   | [38]  |
| 27.2 | Ph₂Sn(CA)₂        | 1087.9                   | 1      | 2.7    |        | 77%    | 0.7   | [38]  |
| 27.3 | Ph₂Sn(CA)₂        | 1087.9                   | 10     | 2.6    |        | 74%    | 1     | [38]  |
| 28.1 | (n-Bu)₂Sn(CA)₂    | 1047.9                   | 0.1    | 3.6    |        | 103%   | 1     | [38]  |
| 28.2 | (n-Bu)₂Sn(CA)₂    | 1047.9                   | 1      | 3.7    |        | 106%   | 1.4   | [38]  |
| 28.3 | (n-Bu)₂Sn(CA)₂    | 1047.9                   | 10     | 3.5    |        | 100%   | 1.3   | [38]  |
| 28.4 | ddH₂O             |                          | -      | 3.5    |        | 100%   | 0.6   | [38]  |
| 29.1 | Pb(NO₃)₂          | 331                      | 0.24   | 50     | 83%   |        | 1     | [36]  |
| 29.2 | Pb(NO₃)₂          | 331                      | 2.41   | 22     | 36%   |        | 2.6   | [36]  |
| 29.3 | Pb(NO₃)₂          | 331                      | 24.1   | 10     | 17%   |        | 3.3   | [36]  |
| 29.4 | control           |                          | 60     |        |       |        |       | [36]  |
| 30.1 | {[SbBr(Me₂DTC)₂]ₙ} | 441.11                   | 0.01   | 10.5   |        | 135%   | 0.7   | [17]  |
| 30.2 | {[SbBr(Me₂DTC)₂]ₙ} | 441.11                   | 0.1    | 10.8   |        | 138%   | 0.5   | [17]  |
| 30.3 | {[SbBr(Me₂DTC)₂]ₙ} | 441.11                   | 1      | 8.4    |        | 108%   | 0.5   | [17]  |
| 31.1 | {[Sb(Me₂DTC)₂]ₙ}   | 499.11                   | 0.01   | 2.6    |        | 33%    | 0.8   | [17]  |
| 31.2 | {[Sb(Me₂DTC)₂]ₙ}   | 499.11                   | 0.1    | 6.4    |        | 82%    | 0.5   | [17]  |
| 31.3 | {[Sb(Me₂DTC)₂]ₙ}   | 499.11                   | 1      | 5.1    |        | 65%    | 1.9   | [17]  |
| 32.1 | {[Me₂DTC]Sb µ₂-I[Sb(Me₂DTC)]₂} | 1232   | 0.01   | 4.4    |        | 56%    | 1.8   | [17]  |
| 32.2 | {[Me₂DTC]Sb µ₂-I[Sb(Me₂DTC)]₂} | 1232   | 0.1    | 8.3    |        | 106%   | 1.2   | [17]  |
| 32.3 | {[Me₂DTC]Sb µ₂-I[Sb(Me₂DTC)]₂} | 1232   | 1      | 1.6    |        | 21%    | 1.7   | [17]  |
| 32.4 | Control           |                          | 7.8    |        |        | 100%   | 0.5   | [17]  |

*1Exposed for 96 h days, *2 mg/L, *3 μg/mL.
(SDM = sulfadimethoxine, phen = 1,10-phenanthroline) have also been evaluated in the same manner. The % MIA values suggest no in vivo toxic behavior in the case of 15.1–15.5 and 16.1–16.5 (Table 1) [32]. However, by taken into consideration the % root length variations, an in vivo toxicity might be proposed for these samples, but the confidence limits of these values exceed or lie to the values themselves (Table 1) [32]. The null % MIA values in the case of samples 17.2–17.5 show in vivo toxicity since there is no cell division [32].

The in vivo toxicity of the samples of Ag(I) complexes with sulfamoxole (SMX), formulae [Ag₂(SMX)₂]·H₂O (18.1–18.5) and [Ag₄(SCN)₃(SMX)]·H₂O (19.1–19.5) was also examined (Table 1). The % MIA values of 58% and 67% suggest that these complexes were toxic at concentrations higher than 81.2 and 25.5 μM, respectively. In addition, the root length was affected at concentrations higher than 32.6 and 6.4 μM, respectively [33].

Gold: The genotoxicity of gold complex [Au(TPP)Cl] (TPP = triphenylphosphine) (20.1–20.3) was tested via A. cepa root cells, in three different concentrations (3 (20.1), 30 (20.2) and 300 (20.3) μM) (Table 1) [34]. The % MIA values of 20.2 and 20.3 were 56% indicating in vivo toxicity, which is also concluded by high % CA values (Table 1) [34].

### Group 14 metals (Sn, Pb) complexes

Organotins: Organotin compounds derived from cholic acid (CAH) R₃Sn(CA) [R = Ph- (25), n-Bu- (26)] and R₂Sn(CA)₂ [R = Ph- (27) and n-Bu- (28)] were evaluated for their in vivo toxicity at the concentrations 0.1 μM (25.1, 26.1, 27.1, 28.1), 1 μM (25.2, 26.2, 27.2, 28.2) and 10 μM (25.3, 26.3, 27.3, 28.3) (Table 1). The diorganotin compounds show no in vivo genotoxicity in contrast to tri-organotin ones. The % MIA in the case of diorganotin is in the range of 74–106% while those of tri-organotin in between 37 and 114% [38].

Lead: The % MIA values of A. cepa cells upon their treatment with 0.24, 2.41 and 24.13 μM Pb ions (in the form of Pb(NO₃)₂) (samples id: 29.1–29.3 respectively) were 82%, 36% and 16% (Table 1). Based on this, the in vivo toxicity of Pb is concluded over 2.41 μM. The corresponding CAs were 1.1%, 2.6% and 3.3% [36].

### Group 15 metals (Sb, Bi) complexes

Antimony: Three antimony compounds with the formulae {[SbBr(Me₂DTC)₂]ₙ} (30), {[SbI(Me₂DTC)₂]ₙ} (31) and {[Me₂DTC]₂Sb(μ₂-I)Sb[Me₂DTC]₂} (32) (Me₂DTC = dimethylthiodiacarbamide) were evaluated for their in vivo toxicity. Samples at concentrations 0.01 (30.1, 31.1, 32.1), 0.10 (30.2, 31.2, 32.2) and 1.00 (30.3, 31.3, 32.3) μM were used (Table 1). The compound of antimony bromide exhibits no genotoxicity (% MIA 108–135% 30.1–30.3) in contrast to antimony iodides (% MIA 33–82% 31.1–31.3 and 21–106% 32.1–32.3 respectively). Consequently, the % CA in the case of samples 31.1–31.3 and 32.1–32.3 is increased. Sticky, bridges and vagrant chromosomes were commonly observed on the samples [17].

### Artemia salina assay

Along with A. cepa, Artemia salina is also a biological model widely used for acute toxicity tests [13] (Fig. 2). The nauplii of the zooplanktonic crustacean is highly sensitive
to contaminants in the aquatic environment [13]. The advantages of the usage of *A. salina* in genotoxicity tests are its short lifetime, its availability, low cost and easy and safe use and its high offspring number [13]. The examined indicators in this assay are the Lethal Concentration (LC50 in mM) or Dose (LD50 in mg/mL) that eliminates the 50% of the nauplii. *A. salina* is considered as dead when it exhibits no any internal or external movement for 10 s of observation [13].

**Group 10 metals (Ni, Pd, Pt) complexes**

Nickel: The LD50 value of nickel metal organic framework (Ni-MOFs) (33) was estimated 138.33 μg/mL (Table 2) [39].

The LD50 value of Ni complex (34) with the Schiff base 3-((4-phenylthiazol-2-ylimino) methyl)-2-hydroxybenzoic acid (L) against brine shrimp was 117.4 μg/mL, while the corresponding value of free ligand was 254.7 μg/mL (Table 2) [40].

The toxicity of Ni complexes with formula \([\text{Ni}_2L^1_2(\mu-1,1-N_3)_2(N_3)_2]·4\text{H}_2\text{O}\) (35), and \([\text{Ni}_2L^2_2(\mu-1,1-N_3)_2(N_3)_2]·6\text{H}_2\text{O}\) (36) \((\text{H}_2\text{L}^1\text{Cl} = (E)-N,N,N\text{-trimethyl-2-oxo-2-(2-(1-(thiazol-2-yl)ethylidene)hydrazinyl)}\text{ethan-1-aminium chloride, H}_2\text{L}^2\text{Cl} = (E)-N,N,N\text{-trimethyl-2-oxo-2-(2-(1-(pyridin-2-yl)ethylidene)hydrazinyl)}\text{ethan-1-aminium chloride}\) exhibit LC50 0.86 and 0.82 mM, respectively (Table 2). The positive control \((\text{K}_2\text{Cr}_2\text{O}_7)\) shows LD50 0.077 mM [41].

The complexes of formulae \([\text{Ni}(L^1)^2\text{Cl}_2] \) \((L^1 = L^1\cdot L^6) \) \([L^1 = \text{N-}(4,6\text{-Dimethylpyrimidine-2-yl})\text{-4-}[\text{furan-2-ylmethylene}]\text{amino}]\text{benzene sulfonamide, L}^2 = 4-\text{[(Furan-2-ylmethylene)]amino}\text{benzene sulfonamide, L}^3 = 4-\text{[(Furan-2-ylmethylene)]amino}\text{ethyl]benzenesulfonamide, L}^4 = 4-\text{[(Furan-2-ylmethylene)]amino}N-(5\text{-methylisoxazol3-yI})\text{benzenesulfonamide, L}^5 = 4-\text{[(5-Methylfuran-2-ylmethylene)]amino}\text{benzenesulfonamide, L}^6 = 4-\text{[(5-Methylfuran-2-ylmethylene)]amino}\text{ethyl]benzenesulfonamide}\) were tested in vivo toxicity. The

Nickel(II) complexes of 2,3-dihydroxybenzaldehyde N4-substituted thiosemicarbazone, \((\text{H}_3\text{L}^1: R = H, \text{H}_3\text{L}^2: R = \text{CH}_3, \text{H}_3\text{L}^3: R = \text{C}_6\text{H}_5\text{ and } \text{H}_3\text{L}^4: R = \text{C}_2\text{H}_5) (43–50)\) show a range of LD50 values between 0.059 to 0.096 mg/mL (Table 2) [43].

The LC50 value is 0.64 mM for Ni(BF_4)2·6H2O (51) (Table 2) [41].

**Group 11 metals (Cu, Ag, Au) complexes**

Copper: The in vivo toxicity of copper complex with amantadine \((\text{AdNH}_2), \{(\text{AdNH}_3)^+\}[\text{CuCl}_3^-] (52)\), was examined through *A. salina* assay. The larvae were exposed to long range of concentrations. The LC50 or LD50 value was determined at 0.428 mM (0.138 mg/mL) (Table 2) [44].

The complexes of formulae \([\text{Cu}(L^1)^2\text{Cl}_2] \) \((L^1 = L^1\cdot L^6) \) \([L^1 = \text{N-}(4,6\text{-Dimethylpyrimidine-2-yl})\text{-4-}[\text{furan-2-ylmethylene}]\text{amino}]\text{benzene sulfonamide, L}^2 = 4-\text{[(Furan-2-ylmethylene)]amino}\text{benzene sulfonamide, L}^3 = 4-\text{[(Furan-2-ylmethylene)]amino}\text{ethyl]benzenesulfonamide, L}^4 = 4-\text{[(Furan-2-ylmethylene)]amino}N-(5\text{-methylisoxazol3-yl})\text{benzenesulfonamide, L}^5 = 4-\text{[(5-Methylfuran-2-ylmethylene)]amino}\text{benzenesulfonamide, L}^6 = 4-\text{[(5-Methylfuran-2-ylmethylene)]amino}\text{ethyl]benzenesulfonamide}\) were tested in vivo toxicity. The
| Code | Molecular formula | Molecular weight (g/mol) | LC50 (mM) | LD50 (mg/mL) | Refs. |
|------|-------------------|--------------------------|-----------|--------------|-------|
| 33   | Ni-MOFs           | -                        | -         | 0.138        | [39]  |
| 34   | [NiL(Cl)2]        | 459.9                    | 0.255     | 0.117        | [34]  |
| 35   | [NiL2·(μ-1,1-N3)2(N3)2]·4H2O | 838.12                  | 0.860     | 0.720        | [41]  |
| 36   | ([NiL2·(μ-1,1-N3)2(N3)2]·6H2O) | 862.09                  | 0.820     | 0.710        | [41]  |
| 37   | [Ni(L2)2Cl2]      | 842.49                   | > 1.19    | > 1.00       | [42]  |
| 38   | [Ni(L2)2Cl2]      | 630.14                   | > 1.59    | > 1.00       | [42]  |
| 39   | [Ni(L2)2Cl2]      | 686.25                   | > 1.46    | > 1.00       | [42]  |
| 40   | [Ni(L5)2Cl2]      | 792.29                   | > 1.26    | > 1.00       | [42]  |
| 41   | [Ni(L5)2Cl2]      | 658.20                   | > 1.52    | > 1.00       | [42]  |
| 42   | [Ni(L5)2Cl2]      | 714.30                   | > 1.93    | > 1.40       | [42]  |
| 43   | [Ni(L5)2Cl2]      | 847.25                   | > 1.19    | > 1.00       | [41]  |
| 44   | [Ni(L5)2Cl2]      | 635.00                   | 0.185     | 0.120        | [41]  |
| 45   | [Ni(L5)2Cl2]      | 691.10                   | 0.182     | 0.130        | [41]  |
| 46   | [Ni(L5)2Cl2]      | 797.14                   | > 1.250   | > 1.00       | [41]  |
| 47   | [Ni(L5)2Cl2]      | 663.05                   | > 1.510   | > 1.00       | [41]  |
| 48   | [Ni(L5)2Cl2]      | 719.16                   | > 1.390   | > 1.00       | [41]  |
| 49   | [Ni(L5)2Cl2]      | 962.56                   | > 1.039   | > 1.00       | [45]  |
| 50   | [Ni(L5)2Cl2]      | 906.46                   | 601       | 545          | [45]  |
| 51   | [Ni(L5)2Cl2]      | 940.51                   | 484       | 455          | [45]  |
| 52   | [Ni(L5)2Cl2]      | 912.46                   | > 1.069   | > 1.00       | [45]  |
| 53   | [Ni(L5)2Cl2]      | 916.54                   | 606       | 555          | [45]  |
| 54   | [Ni(L5)2Cl2]      | 834.39                   | 627       | 523          | [45]  |
| 55   | [Ni(L5)2Cl2]      | 750.31                   | 536       | 402          | [46]  |
| 56   | [Ni(L5)2Cl2]      | 778.36                   | 676       | 526          | [46]  |
| 57   | [Ni(L5)2Cl2]      | 806.42                   | 490       | 395          | [46]  |
| 58   | [Ni(L5)2Cl2]      | 562.4                    | > 1.78    | > 1.00       | [47]  |
| 59   | [Ni(L5)2Cl2]      | 590.4                    | > 1.70    | > 1.00       | [47]  |
| 60   | [Ni(L5)2Cl2]      | 652.4                    | > 31.53   | > 1.00       | [47]  |
| 61   | [Ni(L5)2Cl2]      | 716.5                    | 0.600     | 0.430        | [47]  |
| 62   | [Ni(L5)2Cl2]      | 624.5                    | 0.570     | 0.354        | [47]  |
| 63   | [Ni(L5)2Cl2]      | 594.5                    | > 1.68    | > 1.00       | [47]  |
| 64   | [Ni(L5)2Cl2]      | 772.70                   | 0.012     | 0.004        | [49]  |
| 65   | [Ni(L5)2Cl2]      | 344.70                   | 0.001     | 0.0004       | [49]  |
| 66   | [Ni(L5)2Cl2]      | 357.75                   | 0.002     | 0.0006       | [49]  |
| 67   | [Ni(L5)2Cl2]      | 369.3                    | 0.007     | 0.0027       | [49]  |
| 68   | [Ni(L5)2Cl2]      | 395.27                   | 1.540     | 0.601        | [41]  |
| 69   | [Ni(L5)2Cl2]      | 432.71                   | 1.040     | 0.450        | [41]  |
| 70   | [Ni(L5)2Cl2]      | 878.55                   | 0.460     | 0.404        | [41]  |
| 71   | [Ni(L5)2Cl2]      | 408.71                   | 0.042     | 0.017        | [50]  |
| 72   | [Ni(L5)2Cl2]      | 544.00                   | 0.014     | 0.008        | [50]  |
| Code | Molecular formula | Molecular weight (g/mol) | LC50 (mM) | LD50 (mg/mL) | Refs. |
|------|-------------------|--------------------------|-----------|--------------|-------|
| 86   | [Cu(NCO)₂(INH)₂]·4H₂O | 493.86                  | 0.494     | 0.244        | [50]  |
| 87   | [Cu(L¹)(H₂O)Cl]    | 406.40                  | 1.021     | 0.410        | [51]  |
| 88   | [Cu(L²)(H₂O)Cl]    | 422.04                  | 2.396     | 1.010        | [51]  |
| 89   | [Cu(L³)(H₂O)Cl]    | 386.54                  | > 2.467   | 0.950        | [51]  |
| 90   | [Cu(L⁴)(H₂O)Cl]    | 414.54                  | 0.748     | 0.310        | [51]  |
| 91   | [Cu(L⁵)(H₂O)Cl]    | 379.34                  | > 2.515   | 0.950        | [51]  |
| 92   | [Cu(L⁶)(H₂O)Cl]    | 395.04                  | 1.028     | 0.410        | [51]  |
| 93   | [Cu(L⁷)(H₂O)Cl]    | 358.09                  | > 2.792   | 1.000        | [51]  |
| 94   | [Cu(L⁸)(H₂O)Cl]    | 374.04                  | > 2.674   | 1.000        | [51]  |
| 95   | [Cu(L⁹)(H₂O)Cl]    | 338.54                  | 0.994     | 0.340        | [51]  |
| 96   | [Cu(L¹⁰)(H₂O)Cl]   | 366.54                  | 0.873     | 0.320        | [51]  |
| 97   | [Cu(L¹¹)(H₂O)Cl]   | 331.04                  | > 2.891   | 0.960        | [51]  |
| 98   | [Cu(L¹²)(H₂O)Cl]   | 347.04                  | 1.124     | 0.390        | [51]  |
| 99   | Cu(NO₃)₂·3H₂O      | 241.6                   | 0.240     | 0.060        | [41]  |
| 100  | CuCl₂·2H₂O         | 170.48                  | 0.007     | 0.001        | [49]  |
| 101  | CuCl₂·6H₂O         | 370.54                  | 0.280     | 0.104        | [41]  |
| 102  | ([Ag(pen)(CH₃OH)]₂ | 946.49                  | 532       | 0.504        | [52]  |
| 103  | AgNPs(ORLE)        | -                       | -         | 217.8        | [53]  |
| 104  | [Zn(valp)₂phen(H₂O)] | 551.0                  | 0.142     | 0.078        | [54]  |
| 105  | Zn(valp)₂(bipy)    | 508.98                  | 0.804     | 0.409        | [54]  |
| 106  | [Zn(INH)₃](ClO₄)₂·6H₂O | 646.68                | 268       | 0.174        | [55]  |
| 107  | [ZnL¹(NCS)₂·2H₂O   | 457.85                  | 1.27      | 0.581        | [41]  |
| 108  | [ZnL²(NCS)₂·0.5MeOH | 431.83                  | 0.980     | 0.420        | [41]  |
| 109  | Zn(BF₄)₂·6H₂O      | 347.08                  | 0.880     | 0.310        | [41]  |
| 110  | Zn(OAc)₂·2H₂O      | 587.47                  | 1.180     | 0.690        | [41]  |
| 111  | [CdCl₂(2,3BTSTCH₂)] | 505.65                  | 0.300     | 0.115        | [56]  |
| 112  | [CdBr₂(2,3BTSTCH₂)] | 594.65                  | 0.240     | 0.240        | [56]  |
| 113  | CdHL₁(NCS)₂       | 515.92                  | 0.530     | 0.273        | [41]  |
| 114  | [CdCl₂(aphaOEt)(DMF)] | 955.33                | 3.300     | 3.150        | [57]  |
| 115  | [CdCl₂(dapha(OEt)₂)]·1.5H₂O | 1147.49         | 1.390     | 1.600        | [57]  |
| 116  | CdCl₂             | 183.31                  | 3.030     | 0.560        | [57]  |
| 117  | Cd(NO₃)₂·4H₂O      | 236.42                  | 0.500     | 0.118        | [41]  |
| 25   | PH₃Sn(CA)          | 757.50                  | 0.006     | 0.005        | [38]  |
| 26   | n-BuSn(CA)         | 697.52                  | 0.004     | 0.003        | [38]  |
| 27   | Ph₂Sn(CA)₂         | 1087.91                 | 0.023     | 0.025        | [38]  |
| 28   | (n-Bu)₂Sn(CA)₂     | 1047.92                 | 0.006     | 0.006        | [38]  |
| 118  | [Sn(2Am₄DH)Cl₃]   | 419.28                  | 0.025     | 0.010        | [58]  |
| 119  | [Sn(2Am₄Me)Cl₃]   | 433.31                  | 0.014     | 0.006        | [58]  |
| 120  | [Sn(2Am₄Et)Cl₃]   | 447.36                  | 0.013     | 0.006        | [58]  |
| 121  | [Sn(2Am₄Ph)Cl₃]   | 495.40                  | 0.002     | 0.001        | [58]  |
| 122  | [(n-Bu₂Sn)₂L]     | 816.11                  | 0.032     | 0.039        | [59]  |
| 123  | MeSnCl(dact)       | 458.55                  | 0.081     | 0.037        | [60]  |
| 124  | BuSnCl(dact)       | 500.62                  | 0.133     | 0.061        | [60]  |
| 125  | PhSnCl(dact)       | 520.62                  | 0.040     | 0.018        | [60]  |
| 126  | Ph₂Sn(dact)        | 562.28                  | 0.022     | 0.010        | [60]  |
| 127  | Bu₂Sn(Acac)(4-MePCDT) | 506.28         | 0.165     | 0.084        | [61]  |
LC₅₀ values are in the range of 0.182 to higher than 1.5 mM (Table 2) [42].

The LC₅₀ values of compounds with formulae Cu(L₁–H₂)₂(H₂O)₂ (59–64) (L¹ = N-(4,6-dimethylpyrimidin-2-yl)-4-[(2-hydroxynaphthalen-1-yl)methyleneamino]-benzenesulfonamide, L₂ = N-(pyrimidin-2-yl)-4-[(2-hydroxynaphthalen-1-yl)methyleneamino]-benzenesulfonamide, L₃ = N-(3,4-dimethylisoxazol-5-yl)-4-[(2-hydroxynaphthalen-1-yl)methyleneamino]-benzenesulfonamide, L₄ = N-(5-methylisoxazol-3-yl)-4-[(2-hydroxynaphthalen-1-yl)methyleneamino]-benzenesulfonamide, L₅ = N-(thiazol-2-yl)-4-[(2-hydroxynaphthalen-1-yl)methyleneamino]-benzenesulfonamide, L₆ = N-carbamimidoyl-4-[(2-hydroxynaphthalen-1-yl)methyleneamino]-benzenesulfonamide) toward A. salina assay are in the range of 484 mM to higher than 1000 mM (Table 2) [45].

Complexes of formula Cu(L¹–H₂)₂(H₂O)₂ (65–67) (L¹ = 4-[(2-hydroxynaphthalen-1-yl)methyleneamino-]benzenesulfonamide, L² = 4-[(2-hydroxynaphthalen-1-yl)methyleneamino]benzenesulfonamide and L³ = 4-[(2-hydroxynaphthalen-1-yl)methyleneamino]-ethyl benzenesulfonamide) were used in vivo by A. salina assay. The range of LC₅₀ values is between 490 and 676 mM (Table 2) [46].

The toxicity of copper complexes [CuLCl](NO₃), [CuCl](ClO₄) and [Cu₂L₂(μ-1,1-N₂)₂](ClO₄)₂ (81–83) (H₂LCl = (E)-N,N,N-trimethyl-2-oxo-2-(1-pyridinediyldihyrazinyl)ethyl ether, L = 1-aminomethyl-1-phenol, L⁴ = 2-[(2-(2-Thienyllmethylene) amino)ethyl]imino]-methyl}thienyl, L⁵ = 2-[(2-Thienyllmethylene) amino]phenyl)imino]-methyl]pyrrol, L⁶ = 2-[(2-Thienyllmethylene) amino]phenyl)imino]-methyl]pyrrol, L⁷ = 2-[(2-Furillylmethylene) amino]ethyl]imino]-methyl]pyrrol, L⁸ = 2-[(2-Furillylmethylene) amino]ethyl]imino]-methyl]pyrrol, L⁹ = 2-[(2-Furillylmethylene) amino]ethyl]imino]-methyl]pyrrol, L¹₀ = 2-[(2-Furillylmethylene) amino]ethyl]imino]-methyl]pyrrol, L¹₁ = 2-[(2-Furillylmethylene) amino]ethyl]imino]-methyl]pyrrol, L¹₂ = 2-[(2-Thienyllmethylene) amino]ethyl]imino]-methyl]pyrrol) are between 0.87 to higher than 2.9 mM (Table 2) [51].

Copper salts: The LC₅₀ value is 0.24 mM for Cu(NO₃)₂·3H₂O (99) (Table 2) [41]. Moreover, the LC₅₀ value of CuCl₂·2H₂O (100) was 7.0 μM [49]. The LC₅₀ values of Cu(CIO₄)₂·6H₂O (101) is 0.28 mM (Table 2) [41].

Silver(I): The combination of penicillin G (PenH) with silver(I) ions resulted in the formation of a new metallodrug with the formula [(Ag(pen)(CH₃OH))₂] (102). Its toxicity was evaluated through A. salina assay at a range of concentration 0.04 to 1.05 mM. The LC₅₀ was determined at 0.532 mM (or 0.504 mg/ml) (Table 2) [52].

The extract from oregano leaves (ORLE) was used for the synthesis of silver nanoparticles, AgNPs(ORLE) (103). The tested concentrations were in the range of 150 to 300 mg/mL. The LC₅₀ was determined 217.8 mg/mL (Table 2) [53].
**Group 12 metals (Zn, Cd, Hg) complexes**

Zinc: Two zinc complexes [Zn(valp)_2phen(H_2O)] (104) and Zn(valp)_3(bipy) (105) (valp = valproic acid, phen = 1,10-phenanthroline, bipy = 2,2-bipyridine) show LD_{50} value against A. salina 0.078 and 0.409 mg/mL respectively (Table 2) [54].

The LC_{50} value of compound Zn(INH)_2[CIO_4]_2·6H_2O (106) (INH = isoniazid) was calculated at 268 μM (Table 2) [55].

The LC_{50} values of zinc complexes, [ZnL^1(NCS)_2]·2H_2O (107) and [ZnL^2(NCS)_2]·0.5MeOH (108) (HL^1Cl ligand = (E)-N,N,N-trimethyl-2-oxo-2-(2-(1-((thiazol-2-yl)ethylidene)hydrazinyl)ethan-1-aminium chloride, HL^2Cl = (E)-N,N,N-trimethyl-2-oxo-2-(2-(1-(pyridin-2-yl)ethylidene)hydrazinyl)ethan-1-aminium chloride, NCS = N-Chlorosuccinimide), are calculated at 1.27 and 0.98 mM, respectively (Table 2) [41].

The LD_{50} of zinc salts, Zn(BF_4)_2·6H_2O (109) and Zn(OAc)_2·2H_2O (110), exhibited a range of 0.88 to 1.18 mM (Table 2) [41].

Cadmium complexes of thioene-2,3-dicarboxaldehyde bis(thiosemicarbazone) (2,3BTSTCH_2) with formulae [CdCl_3(2,3BTSTCH_2)] (111) and [CdBr_2(2,3BTSTCH_2)] (112) were assessed through A. salina test. The LC_{50} (or LD_{50}) values were 0.3 mM (or 0.115 mg/mL) (111) and 0.24 (or 0.132 mg/mL) (112) mM, respectively (Table 2) [56].

The LC_{50} value of the complex CdHL^2(NCS)_2 (113) (HL^2Cl = (E)-N,N,N-trimethyl-2-oxo-2-(2-(1-((pyridin-2-yl)ethylidene)hydrazinyl)ethan-1-aminium chloride, NCS = N-Chlorosuccinimide) is 0.53 mM (Table 2) [41].

Cd complexes with derivatives of 2-acetylpyridine ethyl hydrazinoacetate hydrochloride (alphaOEt) or 2,6-diacetylpyridine ethyl hydrazinoacetate hydrochloride (dapha(OEt)_2, formulae CdCl_2(alphaOEt)(DMF) (114) and [CdCl_2(dapha(OEt)_2)]·1.5H_2O (115), show LC_{50} values 3.30 and 1.39 mM, respectively (Table 2) [57].

The LC_{50} value of CdCl_2 (116) is 3.03 mM [57] and 0.50 mM for Cd(NO_3)_2·4H_2O (117) (Table 2) [41].

**Group 14 metals (Sn, Pb) complexes**

Organotins: Organotin compounds derived from cholic acid (CAH), R_3Sn(CA) [R = Ph- (25), n-Bu- (26)] and R_2Sn(CA)_2 [R = Ph- (27) and n-Bu- (28)] were evaluated for their in vivo toward A. cepa and were also studied using A. salina. The range of LC_{50} values are between 3.9 and 23.3 μM (Table 2) [38].

Tin(IV) complexes [Sn(2Am4DH)Cl_3] (118), [Sn(2Am4Me)Cl_3] (119), [Sn(2Am4Et)Cl_3] (120) and [Sn(2Am4Ph)Cl_3] (121) (H_2Am4DH = 2- pyridineformamide thiosemicarbazone, H_2Am4Me = N(4)-methyl 2-pyridineformamide thiosemicarbazone, H_2Am4Ph = N(4)-methyl 2-pyridineformamide thiosemicarbazone, H_2Am4Me = N(4)-methyl 2-pyridineformamide thiosemicarbazone, H_2Am4Ph = N(4)-methyl 2-pyridineformamide thiosemicarbazone) were tested via A. salina assay a LD_{50} value of 83.7 μg/mL (Table 2) [61].

**Table 3** Summary of the most common CAs induced by a specific metal

| Metal | Most common CAs | Refs. |
|-------|-----------------|-------|
| Ag    | Chromosome adherences, chromosome losses, single bridges and fragments | [16, 20, 27–29] |
| Sb    | Stickiness, bridges and vagrant chromosomes | [17, 38] |
| Cd    | Chromosomal bridge, break, stickiness, clumping, c-mitosis, stickiness | [37] |
| Ni    | C-mitosis | [62] |
| Hg    | Stickiness | [62] |

Moreover, the value % Mitotic Index Alteration (%MIA(C)) was introduced to overcome the quality of

**Conclusion**

The biological effects of metal ions and their compounds in the living organisms (A. cepa and A. salina) are reviewed here with the aim on the development of in vivo toxicity models for the evaluation of their genotoxicity and toxicity. To accomplish this goal, their microscopic parameters (such as MI and CA) as well as their macroscopic ones (root length) were reviewed and compared, and the LC_{50} or LD_{50} values are summarized.

The study revealed that some CAs are usually observed after the treatment with a metal ion [16, 17, 20, 27–29, 37, 38, 62] (Table 3). However, a specific abnormality of the chromosomes could not be linked with the presence of a particular metal ion, since different metal ions may promote the appearance of the similar result. In agreement to this, Leme et al. [14] reported previously that the grouping of metal ions regarding their cytological effects is not possible.

Moreover, the value % Mitotic Index Alteration (%MIA(C)) was introduced to overcome the quality of
Fig. 3  %MIA in *A. cepa* root cells induced by exposure to different concentrations of groups 10, 11, 12, 14 and 16
control water used as well as the variety of A. cepa bulb types. A substance could be considered as non-toxic, if it promotes the death of < 30% of the cells (viability ≥ 70%) (ISO 10993-5:2009) [21, 22]. This classification is extended within this work to categorize any agent that caused %MIA(C) ≤ 70% as a potent genotoxic one, with the rests to be considered as a non-genotoxic.

No conclusion can be drawn for the time scale (24 or 48 h) of the effect since no sufficient data are available (Table 1). On the contrary, Jaishankar et al. [63], have reported that metal ion toxicity depends not only on its dosage but on the duration of this exposure as well [63].

Among the metal ions and their compounds of the group of elements studied here, those of 12 show %MIA ≤ 70 against A. cepa at lower concentration (1–10 μM), since they affecting strongest the mitosis of the bulb (Table 1, Fig. 3). However, lacking a large number of samples that would lead to reliable conclusions for the elements of all groups studied the very low toxicity of silver and its compounds can be suggested (%MIA ≤ 70 at 250–600 μM) (Fig. 3).

Comparing the % MIA of silver(I) complexes with various ligands, differences in genotoxicity are observed (Fig. 3). Therefore, the presence of the ligand affects the genotoxicity of the metal ion, as it alters its environment [64]. This is expected since different chemical environment of the metal ion influences the lipophilicity of the complex and, as a consequence, its ability to permeate the cell membrane [65]. Thus, different ligands lead to different absorption and uptake levels in different organs or cell organelles [66]. These differences result in a wide range of toxicity observed. Moreover, the precursor of the gold complexes [Au(tpp)Cl] [20] does not affect the mitotic index up to the concentration of 30 μM. In the case of the tin and antimony complexes, their genotoxicity is induced at the concentrations of 10 and 0.01 μM, respectively.

In the case of *Artemia salina* assay, the mean of LC_{50} values of the complexes is between 0.04 and 126 mM. The most potent toxic compounds seem to be the tin compounds (LC_{50}^{mean} = 0.04 mM, count = 14), while the less toxic seems to be the copper complexes (LC_{50}^{mean} = 126, count = 32). Generally, the toxicity order is Cu < Zn < Cd < Ni < Sn (with LC_{50}^{mean} 126 (Cu), 39 (Zn), 1.3 (Zn), 0.29 (Ni) and 0.04 (Sn) mM).

In conclusion, two biological assays, namely *Allium cepa* and *Artemia salina*, were reviewed regarding the toxicity risk assessment of metal ions. The findings highlight the effect of the metal ions and their complexes in the biological systems, such as plants, aquatic organisms and hence humans. Their toxicity is in high relevance with their concentration. Considering that humankind is continuously dependent on surface waters the contribution of the environmental biological inorganic chemistry toward the refinement of the environment can be of great importance, and it initiates a new era in the field of environmental chemistry and biological sciences.

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**Declarations**

**Conflict of interest** The authors have no competing interests to declare that are relevant to the content of this article.

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