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Which Metals are Green for Catalysis? Comparison of the Toxicities of Ni, Cu, Fe, Pd, Pt, Rh, and Au Salts

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Environmental profiles for the selected metals were compiled on the basis of available data on their biological activities. Analysis of the profiles suggests that the concept of toxic heavy metals and safe nontoxic alternatives based on lighter metals should be re-evaluated. Comparison of the toxicological data indicates that palladium, platinum, and gold compounds, often considered heavy and toxic, may in fact be not so dangerous, whereas complexes of nickel and copper, typically assumed to be green and sustainable alternatives, may possess significant toxicities, which is also greatly affected by the solubility in water and biological fluids. It appears that the development of new catalysts and novel applications should not rely on the existing assumptions concerning toxicity/nontoxicity. Overall, the available experimental data seem insufficient for accurate evaluation of biological activity of these metals and its modulation by the ligands. Without dedicated experimental measurements for particular metal/ligand frameworks, toxicity should not be used as a "selling point" when describing new catalysts.

1. Introduction

Catalysis is a paramount driving force for the development of science and technology in this century. The cutting edge of catalysis has had an unquestionable impact on the chemical industry, materials science, nanotechnology, molecular electronics, pharmaceutical sciences, and various fields of organic, inorganic, and organometallic chemistry. The trend in publication activity clearly highlights the continuous development of new methods and applications (Figure 1 A).

Organic synthesis has been making outstanding recent progress because of the incorporation of transition-metal catalysis into routine laboratory practice.[1] Excellent well-defined catalysts for numerous practical transformations have been created using palladium,[2] platinum,[3] gold,[4] and rhodium[5] complexes. As a result of tremendous recent interest, nickel and iron have emerged as new active players in the field,[6] whereas a renaissance in copper chemistry has facilitated many novel applications.[7]

Re-thinking of environmental reasons and sustainable development are the current key factors in catalysis (Figure 1 B). When we hear about palladium, platinum, and gold, the phrase heavy metal[8] is usually involved, and we typically think about toxicity and contamination. Leaching of transition metals from automotive catalysts is a particular example of critical environmental pollution.[9]

In this regard, nickel, iron, and copper are opposed to toxic metals and are considered to be a green and sustainable alternative. Indeed, nickel, copper, and iron are usually referred to as essential trace nutrients for living organisms,[10] whereas gold, palladium, platinum, and rhodium are discussed more often in terms of toxicity.[11]

At some point the difference between toxic heavy metals and safe alternatives has been taken for granted, and it is still widely used as a motivation for the development of nickel, iron, and copper catalysts as replacements for more toxic metals. However, more detailed analysis has revealed an unexpected picture. In this Minireview, we point out a critical issue: metals that were initially considered benign may be significantly more toxic than conventional heavy metals. Re-evaluation of the common belief concerning toxic/nontoxic

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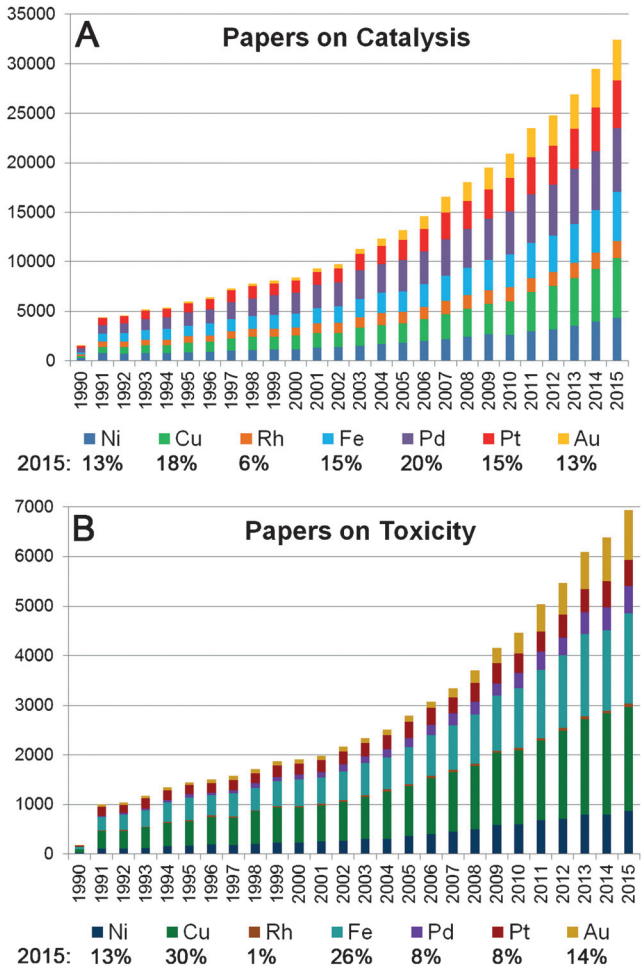

Figure 1. Approximate number of publications dealing with the given metal and catalysis (A) or toxicity (B) in the last 25 years (according to the Web of Science database, www.webofknowledge.com). Proportions of publications on the corresponding metals are shown for the year 2015 (in % within the considered metals).

metal compounds is the key issue for the development of the field of catalysis and for environmental concerns.

2. Ni, Cu, Fe, Pd, Pt, Rh, and Au: Environmental Behavior

Of the seven metals to which this Minireview is dedicated, iron is the most abundant, and its annual production approaches three billion tons. Gold, palladium, platinum, and rhodium are significantly more rare elements, and their production varies from 30 to 3000 tons per year (Table 1). Therefore, the possibility of coming across iron, copper, and nickel dramatically exceeds that of palladium, platinum, and rhodium. Since the toxicity of metal ions and nanoparticles significantly surpasses that of the bulk metal, it is the chemical reactivity that should be taken into account in the first place. Herein we focus on the title topic and discuss possible environmental influences of catalytic reactions.

The phenomenon of leaching has been demonstrated for all types of catalytic systems, including homogenous, heterogeneous, metal-complex, ligand-free, and immobilized catalysts based on transition metals.[9f,12] Leaching results in the generation of M^{n+} ions and sometimes also in the formation of nanoparticles (Figure 2). Even specially immobilized catalysts tend to leach and, in most cases, either change invariably or turn into nanoparticles.[13] The leaching from automotive catalysts causes special concern, since it spreads metal species and particles directly into the environment.[9]

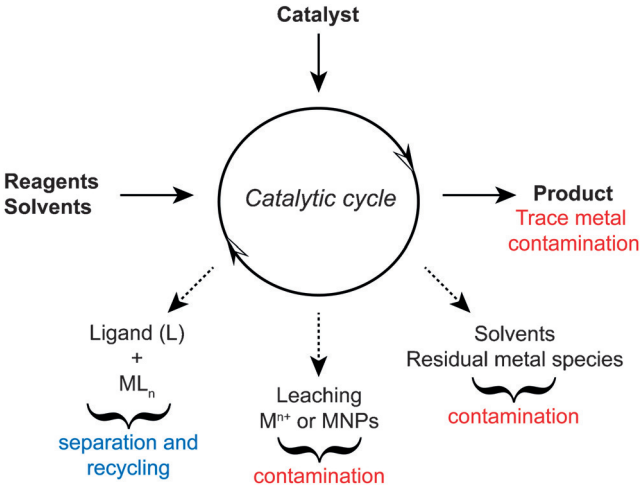

Figure 2. Leaching of metal ions and nanoparticles is a possible source of environmental contamination. MNPs = metal nanoparticles.

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Table 1: Nickel, copper, iron, gold, palladium, platinum, and rhodium: distribution, usage and solubility of simple compounds.

Metal	Distribution in the Earth's crust/seawater, ppm[19]	World production, tons per year (as of 2015)[20]	Usage[17c,20][a]	Solubility of simple compounds g/100 g water[b]
Ni	80/ $1–6\times10^{-4}$	2.5×10^{6}	**Steel production**, **metal alloys**, jewelry, electrolysis, batteries, electrical appliances, welding, chemical industry	$Ni(OAc)_2{\cdot}4H_2O$, 17 (20 °C);[21] $NiCl_2$, 39.6 (25 °C); $NiCl_2{\cdot}6H_2O$, 254 (20 °C);[21] $NiNO_3$, 50 (25 °C); $NiSO_4$, 40.8 (25 °C); $NiCO_3$, 0.0093 (25 °C); $Ni_3(PO_4)_2{\cdot}7H_2O$, insoluble; Ni_2O_3, insoluble
Cu	50/0.8– 2.8×10^{-4}	18.7×10^{6}	**Electrical and thermal conductors**, **industrial materials**, chemical industry	Cu(OAc), rapidly hydrolyses to form Cu_2O; CuCl, slightly soluble; Cu_2O, insoluble; $Cu(OAc)_2{\cdot}H_2O$, soluble; $Cu(acac)_2$, slightly soluble; $CuCl_2$, 43.8 (25 °C); $Cu(NO_3)_2$, 60.1 (25 °C); $CuSO_4$, 18.4 (25 °C); $CuCO_3$, insoluble; $Cu_3(PO_4)_2$, insoluble; $Cu(OH)_2$, insoluble
Fe	41×10^{3}/ $0.1–4\times10^{-4}$	3.3×10^{9}	**Metallurgy**, **construction,** many industrial and technological applications	$Fe(OAc)_2{\cdot}4H_2O$, soluble; $Fe(acac)_2$, slightly soluble; $FeCl_2$, 39.4 (25 °C); $Fe(NO_3)_2{\cdot}6H_2O$, 134 (10 °C); $FeSO_4$, 22.8 (25 °C); $FePO_4{\cdot}2H_2O$, insoluble; $FeCO_3$, 0.0067 (25 °C); FeO, insoluble; $Fe(OH)_2$, 0.00015 (18 °C); $FeCl_3$, 74.4 (0 °C);[21] $FeCl_3{\cdot}6H_2O$, 92 (20 °C);[21] $Fe(NO_3)_3{\cdot}9H_2O$, 137.7 (20 °C); $Fe_2(SO_4)_3$, slowly soluble with hydrolysis; $Fe_3(PO_4)_2{\cdot}8H_2O$, insoluble; Fe_2O_3, insoluble; $Fe(OH)_3$, insoluble
Au	1.1×10^{-3}/ 1×10^{-5}	3000	Jewelry, dentistry, electric appliances, medicine	AuCl, insoluble; $AuCl_3$, soluble; Au_2O_3, insoluble; $Au(OH)_3$, insoluble
Pd	6×10^{-4}/1.9– 6.8×10^{-8}	208	**Automotive catalytic converters**, technical applications, electronics, jewelry, chemical industry	$Pd(OAc)_2$, insoluble; $PdCl_2$, 0.403 (30 °C);[22] $PdCl_2{\cdot}2H_2O$, soluble; $Pd(NO_3)_2$, >1 (30 °C);[22] PdO, insoluble
Pt	1×10^{-3}/1.1– 2.7×10^{-7}	178	**Automotive catalytic converters**, jewelry, technical applications, anticancer drugs, chemical industry	$PtCl_2$, insoluble; $PtCl_4{\cdot}5H_2O$, soluble; $Pt(NO_3)_2$, 0.0141 (30 °C);[22] $Pt(NH_3)_2Cl_2$, 0.0253 (25 °C); PtO, insoluble
Rh	2×10^{-4}/N/A	<30	**Automotive catalytic converters**, glass industry, chemical industry, jewelry, technical applications	$RhCl_3$, insoluble; $RhCl_3{\cdot}xH_2O$ ($x=3–4$), soluble;[23] $Rh_2O_3{\cdot}5H_2O$, insoluble;[23] $Rh(OH)_3$, 0.00001 (30 °C)[22]

[a] Major fields of application are shown in bold. [b] Data from Ref. [24] if not stated otherwise (some data correspond to g in 100 g of solution).

Ligands can be easily isolated from the catalytic systems by using standard methods, such as chromatography, extraction, etc. Metal complexes bound to ligands can also be readily separated after the reaction is done (Figure 2). Therefore, in principle the environmental contamination with ligands or organometallic complexes can be routinely avoided. The most dangerous is the leaching of either metal ions or nanoparticles, which are very difficult to separate from solvents, products, by-products, and wastes. Indeed, trace amounts of metal contaminants are typical impurities in catalytic procedures and represent a well-known problem.

The presence of a metal in the environment does not guarantee the manifestation of its toxicity. To enter the living organism, the metal must be in an appropriate bioavailable form. One of the main factors influencing the environmental dangers of chemical compounds is their solubility in water. Table 1 includes data on the solubility of some simple salts and oxides formed by nickel, copper, iron, gold, palladium, platinum, and rhodium.

Still, good water solubility is also not enough for the component to become bioavailable. Another factor influencing the environmental hazard of the compound is its transformation within the environment. Thus, when soluble metal salts get into water, they may give M^{n+} ions, which could undergo complexation, precipitation, or adsorption. Most metal ions interact with hydroxy and carbonate ions, as well as with some other available inorganic and organic ions. If a stable and nonsoluble complex is formed, such a transformation will reduce the metal toxicity. Insoluble complexes precipitate or form sediments, and these processes depend strongly on the water system, pH, and other conditions.[14] For example, iron salts are involved as Lewis acids in various catalytic reactions.[15] In aqueous media, the inorganic Fe^{3+} salts are prone to hydrolysis with formation of insoluble iron oxides and hydroxides. In the case of $FeCl_3$, hydrogen chloride is produced during hydrolysis.[16] Therefore, it is natural to expect the toxicity of a metal to depend on its valence state, particle size, and coordination sphere, all of which influence its solubility and choice of cellular transporters carrying it into the cell.

3. Mechanisms of Toxicity: General Aspects

Mechanisms which underlie the biological activity of metals have been extensively studied, and a significant

amount of data has been accumulated.[17] There is no single parameter to describe the general toxicity of a metal because toxic manifestations are the result of multiparameter actions which depend strongly on the route of exposure, bioavailability, solubility, metal oxidation state, ligand, dose, etc.[18]

There are several ways by which metal uptake proceeds in animals: by ingestion, by inhalation, and by absorption through the skin. Once in the digestive tract, the metal can be absorbed by diffusion or, in some cases, by active transporters. In the airways, it also can be absorbed by diffusion or can deposit on the mucous membranes. After absorption, the metal gets into the blood, where it often binds to specific proteins which may impact its distribution and toxicity. Finally, the metals may be deposited within some organs or may be excreted with feces, urine, bile, saliva, or sweat.[17c]

As we have already mentioned, water solubility is only one of the factors which define bioavailability and respective toxicity of a substance. The solubility of a compound in pure water may differ from that in biological fluids,[25] and the substance bioavailability also depends on mechanisms of its uptake and clearance from the organism.[10d] According to the bioavailability model, which explains the carcinogenic potential of metals by the example of soluble and insoluble compounds of nickel, soluble salts are not necessarily carcinogenic, whereas insoluble particles may possess remarkably high tumorigenicity.[26] Carcinogenicity may depend on the ability of a substance to enter the cell by endocytosis: the particles which undergo endocytosis end up in lysosomes where their dissolution occurs and the resulting metal ions are released into the cytoplasm and penetrate into the nucleus, thus leading to chromatin damage and neoplastic transformation. Contrariwise, soluble salts release metal ions outside the cell, where they interact with proteins or amino acids and enter the cytoplasm through membrane channels as complexes, which cannot be delivered into the nucleus.[25c,26,27]

Therefore, when assessing the toxic potential of a substance, comprehensive analysis of its properties and transformations within the environment and inside the living organism is required.

4. Toxicity Parameters

In this section, before comparing toxicity data, we will briefly outline parameters which are commonly used to assess the environmental impact of chemicals. A material safety data sheet (MSDS) for each chemical compound contains basic data on its toxicity. Usually it includes information on acute oral, dermal, intravenous, or intraperitoneal toxicity, inhalation toxicity, skin/eye irritation, reproductive toxicity, and carcinogenicity in rodents and humans. There can also be information on cytotoxicity obtained in various cell cultures. There are often data regarding environmental toxicity towards fish, aquatic invertebrates (usually the water flea *Daphnia magna*), and algae.

Oral, intravenous, and intraperitoneal toxicities are measured as LD_{50} or LC_{50} values (median lethal dose or median lethal concentration, respectively), which represent a dose that kills half the members of a test population.[28] This parameter is usually expressed in grams per kilogram of body weight or grams per liter.

Skin and eye irritation,[29] as well as reproductive toxicity and carcinogenicity,[30] are commonly described in qualitative terms of reaction severity (e.g., mild/severe irritation, presumed reproductive toxicant, etc.), although sometimes EC_{50} or IC_{50} values (half maximal effective concentration or half maximal inhibitory concentration, respectively; moles or grams per liter) are mentioned.

Cytotoxicity is measured using standard tests, such as the MTT assay, which is based on determination of the activity of cellular dehydrogenases and correlates directly with cell viability.[31] Chemical cytotoxicity is usually given as EC_{50} or IC_{50} values, that is, the concentration at which a chemical kills half the population of test cells. Environmental toxicity is estimated as effects on fish, aquatic invertebrates, and algae and is studied by various techniques. For example, in the case of *Daphnia magna*, acute immobilization and reproduction tests are used, and the results are expressed as EC_{50} or IC_{50} values.[32] When assessing the toxicity of chemicals, it should be remembered that lower LD_{50}, LC_{50}, EC_{50}, and IC_{50} values correspond to more toxic substances. For example, the lower the LD_{50} value of a given chemical the less it takes to produce a toxic effect.

It should be noted that the number of publications regarding toxicity issues of the considered metals does not always correlate with the number of studies dealing with catalysis. Some of the metals, such as rhodium, palladium, and platinum, are noticeably understudied in comparison to their practical potential (Figure 1).

5. Toxicity of Ni, Cu, Fe, Pd, Pt, Rh, and Au Salts

In Table 2, we collected representative data on the toxicity of metal salts which are commonly used for the preparation of catalysts. These data were obtained from MSDSs (Sigma–Aldrich),[33] the WHO numerical list of environmental health criteria,[34] and original research papers.

According to the MSDS data on rat oral toxicity (Table 2, bold numbers), $NiCl_2$ is the most toxic compound of all the salts listed, whereas $PtCl_2$ is the least toxic compound. $PtCl_4$ is significantly more toxic than $PtCl_2$, as evidenced by rat oral and intraperitoneal LD_{50} values, and is more toxic than chlorides of copper, iron, gold, and rhodium, whereas a wide range is given for LD_{50} of $PdCl_2$. In general, we can range the salts according to their toxicities as follows: $NiCl_2 > PdCl_2 > PtCl_4 > CuCl_2 \approx AuCl_3 > FeCl_3 > RhCl_3 > PdCl_2 > PtCl_2$, with $PdCl_2$ taking an uncertain place between $NiCl_2$ and $PtCl_2$ because of variations in the reported values. If we look at the data on rat oral toxicity from both the WHO and individual publications, the picture is different (Table 2): $CuCl_2 > PdCl_2 > PtCl_4 > FeCl_3 > NiCl_2 > [PdCl_2] > RhCl_3 > PtCl_2$. Still, in both cases $RhCl_3$ and $PtCl_2$ are the least toxic chemicals, whereas the salts of nickel and copper are more toxic.

The data obtained in several test models with different organisms generally support the trend:

Table 2: Selected toxicology data on metal salts typically used for catalyst preparation.[a,b]

Metal salt	Rat (oral), LD_{50} [mg kg^{-1}]		Rat (i.p.), LD_{50} [mg kg^{-1}]	Chick embryo, mg/egg	*Daphnia magna*, LC_{50} [μg L^{-1}]	MC3T3-E1 cell line, IC_{50} [μM]	L929 cell line, IC_{50} [μM]
$NiCl_2$	**[105], 186**	[500][39]	11[40]	[0.2][41]	[130][42]	[52.2][43]	[106][43]
$CuCl_2$	**[336], 584**	[66],[44] 140[34,45]		[0.6][41]	44[42]	[15.9][43]	[41.5][43]
$FeCl_3$	**[900]**	[450][35]			[5900][42]	[328][43]	[5420][43]
$PdCl_2$	**200–2704**	200,[46] [575][47a]	[85–128],[47a] 70[46]	[> 20][41]		588[43]	174[43]
$PtCl_2$	**3423**	> 1330/3423[34,47a]	670[34]				
$PtCl_4$	**276**	240–276[34]	38[34]	{0.13}[41]	{520}[42]		
$RhCl_3$	**1302**	1302[48]		> 10[41]		[21.4][43]	[407][43]
$AuCl_3$	**{> 464}**			{> 20}[41]	{1050}[42]		

[a] Data within square brackets correspond to crystallohydrates ($NiCl_2{\cdot}6\,H_2O$, $CuCl_2{\cdot}2\,H_2O$, $FeCl_3{\cdot}6\,H_2O$, $PdCl_2{\cdot}2\,H_2O$, $RhCl_3{\cdot}3\,H_2O$); data within curly brackets correspond to metal salts containing water and other ligands ($PtCl_4{\cdot}2\,HCl{\cdot}6\,H_2O$, $AuCl_3{\cdot}HCl{\cdot}x\,H_2O$). Data shown in bold were taken from Sigma-Aldrich MSDSs.[33] Values given for a metal amount were recalculated for an amount of a particular salt where needed. [b] Toxicology data details: chick embryo: 4-day toxicity; *Daphnia magna*: 3-week toxicity; MC3T3-E1 (osteoblasts from murine calvaria) and L929 (murine fibroblasts) cell lines: 8-day toxicity.

Rat peritoneal: $NiCl_2 > PtCl_4 > PdCl_2 > PtCl_2$;
Chick embryo: $PtCl_4 \approx NiCl_2 \approx CuCl_2 > RhCl_3 \approx PdCl_2 \approx AuCl_3$;
Daphnia magna: $CuCl_2 > NiCl_2 > PtCl_4 > AuCl_3 > FeCl_3$;
Murine osteoblasts: $CuCl_2 > RhCl_3 > NiCl_2 > FeCl_3 > PdCl_2$;
Murine fibroblasts: $CuCl_2 > NiCl_2 > PdCl_2 > RhCl_3 > FeCl_3$.

It can be clearly seen that in most cases, chlorides of nickel and copper are among the most toxic compounds, whereas chlorides of the traditional heavy metals rhodium and platinum are characterized by higher LD_{50} (LC_{50}, IC_{50}) values. To illustrate the relative toxicity, a graphical representation is given in Figure 3.

Apparently, other salts of nickel and copper are also toxic, thus, the rat oral LD_{50} values of $Ni(OAc)_2$ and $Cu(OAc)_2$ are about 350 and 595 mg kg^{-1}, respectively,[34] which are higher than the LD_{50} values for $NiCl_2$ and $CuCl_2$, but lower than those for $PtCl_2$ and $RhCl_3$. The data available on the toxicity of acetates, acetylacetonates, and sulfates of the metals under discussion are provided in Table 3.

According to the MSDSs, CuCl is more toxic than $CuCl_2$ (rat oral LD_{50} = 336 and 584 mg kg^{-1}, respectively). However, in the cases of $FeCl_2$ and $FeCl_3$, the data are controversial,

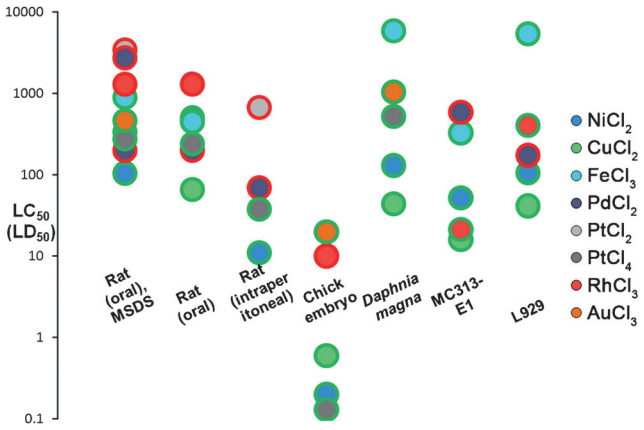

Figure 3. Graphic overview of toxicology data for specified organisms (Table 2), where the *Y* axis shows LD_{50} (LC_{50}, IC_{50}) values on a logarithmic scale. The color of the rim of the circle reflects the salt solubility in water: green = high solubility and red = low solubility.

Table 3: Available toxicology data on acetates, acetylacetonates, and sulfates of selected metals.[a]

Salt	Rat (oral), LD_{50} [mg kg^{-1}]	Rat (i.p.), LD_{50} [mg kg^{-1}]
$Ni(OAc)_2$	350[34]	23[34]
$Ni(OAc)_2{\cdot}4\,H_2O$	550[39]/**350**	
$Cu(OAc)_2$	595[34]/**501**	
$Cu(OAc)_2{\cdot}H_2O$	710[34]/**300–2000**	
$NiSO_4{\cdot}6\,H_2O$	**361**	
$CuSO_4$	300[34]/**482**	150.7 (48 h)[61]/**20**
$CuSO_4{\cdot}5\,H_2O$	960[34]	
$PdSO_4$	> 1420 (14 d)[34]	> 120 (14 d)[34]
$Pt(SO_4)_2{\cdot}4\,H_2O$	1010[34]	138–310[34]
$Fe(acac)_3$	**1872**	
$Pd(acac)_2$	> **2000**	

[a] Data shown in bold were taken from Sigma-Aldrich MSDSs.[33] Values given for a metal amount were recalculated for an amount of a particular salt where needed.

because according to the MSDSs, the former is more toxic than the latter (rat oral LD_{50} 450 and 900 mg kg^{-1} for $FeCl_2$ and $FeCl_3{\cdot}6\,H_2O$, respectively), whereas other sources mention different values (rat oral LD_{50} 450 mg kg^{-1} for both $FeCl_2{\cdot}4\,H_2O$ and $FeCl_3{\cdot}6\,H_2O$[35] and 600 mg kg^{-1} for $FeCl_2$[36]). For reference, MSDSs on the rat oral LD_{50} value for the following common salts are: NaCl, 3550 mg kg^{-1}; $CaCl_2$, 2301 mg kg^{-1}; NaOAc, 3530 mg kg^{-1}; KOAc, 3250 mg kg^{-1}; K_2SO_4, 6600 mg kg^{-1}; $CaSO_4$, > 1581 mg kg^{-1}.[33] In this regard, some of the heavy metal salts, such as $PtCl_2$ and $RhCl_3$, may possess a similar level of toxicity as the above common salts (Table 2).

Since solubility in water is an important factor impacting on the toxicity of chemical compounds, it is unsurprising that soluble salts often exhibit higher toxicity than insoluble ones (Figure 3). Thus, insoluble $PtCl_2$ and $RhCl_3$ show significantly higher oral LD_{50} values than soluble chlorides of nickel, copper, iron, and platinum. Although there is no direct correlation between the solubility and toxicity (probably, because of the different nature of metals and/or inaccuracy in the available data), a general trend obviously exists.

It should also be kept in mind that the biological activity manifested by a chemical depends on the biological object

(organism). This effect has been repeatedly demonstrated for various chemical substances,[37] and the metal compounds are not an exception. Differences in physiological indices between standard laboratory animals and human may cause variations in toxic action of a compound. For example, pH values in stomachs and intestines of rats and mice differ from that in humans, thus implying differences in the formation of metal species.[38]

6. Nanoparticles

As a result of a recent burst of interest in nanocatalysis, many modern catalysts are composed of nanoparticles, and the issue of nanoparticle toxicity has been attracting much attention. Several reviews on nanoparticle release and interaction with the environment, as well as on nanoparticle toxicity, have been published recently.[49]

It is supposed that biological activity of nanoparticles depends both on their size and composition. According to the existing concept, the uptake route of nanoparticles may be governed by their size, shape, and surface properties. However, other characteristics, such as chemical composition, solubility, hydrophobicity, and hydrophilicity, may also play a significant role in the uptake process.[50] Partial dissolution and release of metal ions from solid material may invoke various responses in biological objects.[49b] Therefore, the complexity of interactions of all these factors hinders studies on mechanisms of nanoparticle toxicity.

Gold nanoparticles are widely used in cancer diagnostics and therapy,[51] however, for nanoparticles of other metals, bioactivity data are limited. The toxicity of gold nanoparticles depends on their size and shape,[52] thus, Au_{55} nanoclusters showed high toxicity towards cancerous and healthy human cell lines, apparently because of an interaction with the major groove of DNA.[52a,53]

Gold and iron nanoparticles induced autophagy in various cell cultures.[54] Iron oxide nanoparticles accumulated in various organs, including the brain, liver, spleen, and lungs, entered into cells and released free iron, which might intervene with the cellular iron metabolism.[55]

One report suggested that both gold and copper nanoparticles manifested antimicrobial properties.[56] However, according to other sources, platinum and gold nanoparticles were nontoxic towards bacteria, whereas AuPt bimetallic nanoparticles possessed strong antibacterial activity but did not affect the viability of human umbilical vein endothelial cells (HUVECs).[57] Interestingly, platinum nanoparticles were shown to release no platinum ions and imposed no toxic effect when tested in A549 and HaCaT cells.[58] Platinum nanoparticles also demonstrated no adverse effects in primary keratinocytes,[59] but caused DNA damage in HT-29 cells, though the effect seemed not to be associated with the production of reactive oxygen species (ROS).[60] The toxic effect of platinum nanoparticles appeared to be size-dependent. Thus, platinum sub-nanoparticles (<1 nm) were nephrotoxic and cytotoxic, whereas 8 nm particles demonstrated no toxicity.[62]

In some cases, nanoparticles of metals demonstrated comparable or higher toxicities than their soluble salts. Thus, the mouse oral LD_{50} values for copper nanoparticles, copper microparticles, and cupric ions ($CuCl_2{\cdot}2H_2O$) were 413, >5000, and 110 mg kg^{-1} body weight, respectively, and copper nanoparticles caused injuries in the liver, spleen, and kidney.[63] Cytotoxicity of CuO nanoparticles was attributed to their higher solubility in the lysosomal environment, as compared to that of CuO microparticles.[25c]

In one study on the worm *Enchytraeus albidus*, copper nanoparticles were more toxic than cupric ions ($CuCl_2$). The authors suggested that this effect was not related to the ion release and was therefore size specific.[64]

In other studies, nickel and copper nanoparticles were highly toxic towards *Daphnia pulex*,[65] whereas palladium and platinum nanoparticles exhibited low toxicities towards *Daphnia magna*.[66] However, palladium nanoparticles were demonstrated to possess cytotoxic and antimicrobial activities, and were suggested to be useful in cancer therapy.[67] Palladium nanoparticles disturbed the cell cycle progression in peripheral blood mononuclear cells, possibly because of formation of Pd^{IV} ions.[68]

Nickel nanoparticles are genotoxic and are able to trigger apoptosis in cell cultures in vitro, possibly by inducing generation of oxygen radicals.[50,69] Toxicity of NiO nanoparticles depended on their morphology and, probably, solubility. Thus, nanosized NiO particles demonstrated higher cytotoxicity than fine NiO particles.[70] The association of toxicity with the release of Ni^{2+} ions was also demonstrated for nickel microparticles.[71]

It should be noted that once released into the environment, the nanoparticles may undergo various transformations.[9,49] Therefore, apart from studying toxicity of nanoparticles, which are used in modern laboratory and industrial chemistry, attention also should be paid to the routes of their transformation in nature. Available data on subchronic and chronic toxicity of nickel, copper, iron, gold, palladium, and platinum nanoparticles are summarized in the next section.

7. Chronic Toxicity in Humans

There are three main types of exposure to a chemical compound: inhalative (with fumes or dust), oral (with food or water), and dermal (through contact). Toxic effects depend strongly on the exposure type and exposure period. Thus, acute (1 day exposure), subchronic (10–100 day exposure), and chronic (>100 day exposure) effects may be observed and may manifest as systemic, reproductive, carcinogenic, developmental, or other malfunctions.[72] Information on acute and environmental toxicity gives us some useful information, however, from the point of view of a human population, chronic toxicity is the most important issue. According to the collection for occupational health and safety data, which is issued by the Deutsche Forschungsgemeinschaft,[73] inhalable nickel compounds, including metallic nickel and soluble salts, belong to category 1 of carcinogenic substances, which means that their carcinogenic potential has been established. Iron oxides and inorganic compounds of

rhodium are classified as category 3B, which means that some evidence on carcinogenic properties has been obtained in vitro or in animal studies. Water-soluble nickel compounds and chloroplatinates also present danger of sensitization of the airways and skin. Palladium(II) chloride and other bioavailable palladium(II) compounds, as well as soluble inorganic compounds of gold, present danger of sensitization of the skin.[73]

In this section, we briefly discuss the important factors concerning long-term adverse effects of nickel, copper, iron, gold, palladium, platinum, and rhodium on the human organism.

7.1. Nickel

Nickel and its compounds mainly enter the human organism with food and drinking water.[72,74] However, absorption of nickel from the digestive system is poor, and pulmonary absorption is considered the most dangerous route of entrance. It was shown that 3–6% Ni was absorbed from the digestive tract into the plasma in rats or mice, whereas 35% of inhaled nickel was absorbed from the respiratory tract in humans. The remaining 65% might be partially removed from the airways with mucus and subsequently enter the gastrointestinal tract. In the plasma, Ni^{2+} binds to albumin, amino acids, and small polypeptides. The highest concentrations of nickel are found in the kidney, lung, liver, and endocrine glands. Non-absorbed nickel is removed with feces, and absorbed nickel is mainly eliminated with urine. Nickel carbonyl may penetrate into the brain because of its lipid solubility, whereas insoluble nickel oxide may be retained in the lungs.[17c,72,75]

Occupational exposure to nickel is mainly realized by inhalation and, less often, by dermal contact. Nickel may be inhaled as dust (insoluble compounds), aerosol (soluble compounds), or gas (nickel carbonyl).[76] The chemical form and the size and shape of particles may affect the absorption.[72] Thus, inhalation of nickel nanoparticles caused the death of a healthy 38 year old male as a consequence of acute respiratory distress syndrome.[77] Soluble and particulate nickel was shown to induce lung tumors in exposed workers. Inhalation of particulate nickel(II) also induced tumors in the lung of rodents. The possible mode of action of these compounds is by phagocytosis: insoluble nickel particles accumulate in the cells, dissolve gradually, and release metal ions.[18,26,27]

Nickel was found to be one of the most common metals present in welding fumes, long-time exposure to which correlated with severe pulmonary injury.[78] According to the report on six-week exposure to nickel while welding high-Ni alloy, the workers suffered from airway irritations, headaches, and tiredness.[79] Occupational exposure to nickel correlated with increased rates of pulmonary and nasal cavity cancer,[72] and increased rates of miscarriages and structural malformations in infants was observed for women employed at a nickel metallurgy plant.[80]

Dermal absorption of nickel compounds is poor, though some of them, such as $NiCl_2$, may penetrate the skin efficiently. Allergic skin reactions are thought to be the commonest adverse health effect of nickel in humans.[72,81] A case of sensitization of a chemist by nickel nanoparticles was reported.[82]

Studies in animals corroborate the observations on nickel chronic toxicity. Two-year supplementation of a diet of rats and dogs with $NiSO_4{\cdot}6H_2O$ resulted in growth depression,[83] whereas two-week intraperitoneal injection of mice with $NiCl_2$ led to increased ROS generation and DNA fragmentation in the peripheral blood mononuclear cells.[84] Soluble salts of nickel demonstrated pronounced reproductive toxicity,[85] and exposure to $NiCl_2{\cdot}6H_2O$ was found to increase the rate of fetal malformations in mice.[86] Chronic exposure to nickel nanoparticles also caused reproductive toxicity in rats.[87] NiO and $Ni(OH)_2$ nanoparticles induced chronic inflammation in the lung of rats[88] and mice,[89] and supposedly, both dissolved nickel ions and solid particles contributed to the inflammatory reaction.[89a]

Nickel is a carcinogenic metal, but its carcinogenicity depends on the solubility and capability of nickel ions to penetrate into the cell. Insoluble nickel compounds seemed more prone to invoke cancer than soluble salts of nickel.[10b,c,26,27] Nevertheless, $NiSO_4$ was able to trigger a cancer-related cascade of gene expression in human cells.[90] Moreover, nickel was shown to induce oxidative stress and to bind strongly to proteins, particularly those involved in its transport.[10b,c,91] Recent data suggest that nickel may possess epigenomic activity and may affect modifications of histones.[92]

7.2. Copper

Copper is one of essential microelements for prokaryotes and eukaryotes alike. Normally, copper is required for brain development, and both copper excess and deficiency may lead to severe disorders.[93] Numerous copper-containing enzymes play roles in redox catalyst.[14]

Copper mainly enters the human organism through the digestive system (with food and drinking water), though, as in the case of nickel, inhalation and dermal absorption also may present important exposure types.[94] Absorption and elimination of copper depends on such factors as its chemical form and availability of other dietary elements. About 40% of the ingested copper is absorbed in the small intestine.[95] The human organism assimilates copper in the form of Cu^+, and a family of metalloreductases expressed in the duodenum supposedly reduces both Fe^{3+} and Cu^{2+} ions. Then special transporter proteins assist the Cu^+ transport through the apical membrane of intestine cells. Inside the cell, copper is bound to chaperone proteins and is delivered into the trans-Golgi network.[96]

Copper may be deposited in the liver, which is the main target of its chronic toxicity displayed as liver cirrhosis.[95] Thus, in the case of Tyrolean infantile cirrhosis and Indian childhood cirrhosis, strong contamination of cow's milk with copper from vessels promoted the development of hepatic copper toxicosis.[97] Copper also accumulates in the kidney, spleen, and brain.[17c]

One of the special cases of chronic copper exposure is Wilson's disease, an autosomal recessive metabolic disorder, which is accompanied by increased levels of copper in the liver and brain. In patients with Wilson's disease, disturbance in the normal excretion of copper with the bile results in accumulation of the excess copper in the liver, where it causes oxidative damage and subsequently penetrates into the blood affecting the brain, kidney, and red blood cells.[17c,95,98] Excess copper impacts the lipid profile, inhibits protein sulfhydryl groups, and causes oxidative stress leading to kidney failure.[10a,99]

Allergic reactions to copper are supposed to be infrequent.[100] A case of elemental copper inhalation was described, and resulted in the development of acute respiratory distress syndrome.[101] Copper nanoparticles were demonstrated to provoke inflammation in the rat lung[88a] and to induce injury in the murine liver, spleen, and kidney.[63]

Cu^{1+}/Cu^{2+} were found to coordinate to β-amyloid peptides and to take part in generation of ROS in Alzheimer's disease.[102] Copper increased the β-amyloid production in the brain which resulted in oxidative stress, neuronal apoptosis, and memory impairment. A two-month exposure to copper induced Alzheimer's disease-like neurodegenerative pathology in the rat model.[103]

Of note, copper is essential for angiogenesis, which is an important factor of tumor development.[10h] Because of its high oxidative potential, copper may possess carcinogenic activity, and several types of tumors demonstrate elevated levels of copper.[104]

7.3. Iron

Iron is also an essential microelement and mainly enters the human organism with food, in either the nonheme or heme form. Nonheme iron comes from plant tissues and consists of iron(III), whereas heme iron(II) comes from animal tissues. To be absorbed by the duodenum, Fe^{3+} must be reduced to Fe^{2+}.

Iron species may participate in redox reactions generating harmful ROS, and protection from these dangerous processes is provided by protein ligands, such as transferrin, lactoferrin, and ferritin, which sustain iron in a soluble form. In humans, 68% iron is bound to hemoglobin, 27% to tissue ferritin, and 5% to myoglobin, whereas 0.8% is associated with serum transferrin.[17c] The main site of iron storage is the liver, where iron excess is bound by ferritin. Cells also contain a pool of free iron, which participates in intracellular redox reactions.[105] Iron is eliminated with exfoliated intestinal epithelium, urea, and bile, or through the skin.[106]

There is no special physiological mechanism for elimination of excess iron in the human organism, and it may be highly toxic. Long-term intake of iron supplements or some diseases may lead to chronic iron overload. If the binding capacity of transferrin for iron is overwhelmed, accumulation of free iron in tissues results in damage of the liver, pancreas, heart, and other organs. However, the pathology of iron excess is significantly less studied than that of the iron deficiency, and iron toxicity is often overlooked. Thus, multiple blood transfusions may present significant danger to patients.[105a,107] Among the symptoms of iron intoxication are heart failure, cirrhosis, anemia, and arthritis.[108]

Iron is present in the air as a pollutant. Agglomerates of particulate matter from welding fumes may be deposited in the lungs, and iron, chromium, and nickel are among the most common metals in these particles. Long-time exposure to metal fumes possibly leads to significant pulmonary injury.[78] Bioavailable iron was suggested to be an active component in the coal dust, which induced oxidative stress in human lung epithelial cells.[109] Fe_3O_4 dust showed subchronic inhalation toxicity in rats.[110]

Accumulation of excess iron in the liver leads to mitochondria swelling and rupture.[111] Possible outcomes of iron overload are hepatocellular necrosis and carcinoma,[107b] which may be the result of free radical peroxidative reactions.[107b,108,112] Mitochondria are considered to be especially vulnerable to iron, and mitochondrial distortion leads to other pathological consequences.[112] It was demonstrated that dietary carbonyl iron caused hepatic mitochondrial lipid peroxidation.[113]

Cardiomyocytes are very sensitive to free iron, and its excess may result in congestive cardiomyopathy and disturbed ventricular function. Iron excess also impairs endocrine organs, such as the pancreas, thyroid gland, testes, and ovaries. Among other symptoms of iron overload are arthropathy, osteoporosis, muscle cramps, and myalgia.[107b] Excess of iron induces neurodegenerative disorders through necrosis, apoptosis, and autophagy in the brain.[108]

7.4. Gold

Since there is no clearly established physiological role for gold, platinum, palladium, and rhodium, apart from mechanisms of action of cisplatin and other platinum-based drugs, the data on the routes of migration and transformation of these metals in the organism of higher animals are rather scarce.

Gold is readily absorbed through the digestive tract or skin only when complexed with lipid-soluble ligands. It seems that inhalation of gold does not impair the respiratory tract.[17c] Most cases of gold intoxication are the result of medical overdosage, because this element is recognized in medicine. Thus, $K[Au(CN)_2]$ was initially used by Robert Koch for treatment of tuberculosis.[10h] Gold is a part of modern drugs which possess anti-inflammatory activity, and are employed for treatment of rheumatoid arthritis, Crohn's disease, ulcerative colitis, bronchial asthma, and other disorders, as well as various cancers.[11a]

Gold may accumulate in the liver, bone marrow, bones, skin, and muscles, and its overdose was shown to produce pulmonary and renal damage.[11a,17c] Five-year treatment of rheumatoid arthritis with gold sodium thioglucoside led to accumulation of dense gold microneedles in lysosomes in bone marrow cells, alveolar macrophages, and Kupfer cells. Gold deposits were also found in other organs, such as the eyes and lymph nodes.[11a]

The most common reaction to chrysotherapy is dermatitis.[11a] Thus, salts of gold(I) used for treatment of rheumatoid arthritis were shown to cause immunosensitization, and cases of contact allergy to jewelry and dental fixtures, as well as occupational allergy, were reported.[100,114]

Gold nanoparticles demonstrated subchronic toxicity and adverse effects in the kidney tissue in mice,[115] as well as subchronic inhalation toxicity in rats.[116] Chronic administration of 10 and 30 nm gold nanoparticles led to DNA damage in the cerebral cortex of rats.[117]

The exact mechanisms of gold action remain elusive, however, several hypotheses have been established. For example, in lysosomes of macrophages Au^{+} is oxidized to Au^{3+}, which, in turn, can activate lymphocyte proliferation. An Au^{+}/Au^{3+} redox system which removes ROS may exist in phagocytes. Interestingly, gold(III) compounds exhibited higher activity against cisplatin-resistant cells than the corresponding analogues with either palladium(II) or platinum(II),[10e] whereas some gold-containing compounds could modulate the expression of pro-inflammatory cytokines.[11a]

7.5. Palladium, Platinum, and Rhodium

Usage of palladium, platinum, and rhodium in automobile catalytic converters results in their propagation in the environment and brings these rare elements into contact with the human organism.[9f,g] These metals accumulate in airborne particulate matter, dust, soil, and water. Whereas the metallic form of palladium, platinum, and rhodium is considered biologically inert, some salts of these elements are strong allergens and sensitizers. Thus, though palladium, platinum and rhodium are initially released as metallic and oxide particles, subsequently they may transform within the environment, digestive tract, or cellular compartments and generate more harmful soluble species.[49a,118] Initially, the toxicity of the airborne particulate matter was considered to be primarily associated with the particle size, however, the accumulated evidence suggests that the composition is one of the main factors determining its health hazards.[118b]

Food and water are thought to be important routes of exposure of the platinum-group metals. Still, the inhalation route is supposed to present a greater risk of adverse health effects.[118b] The metals were suggested to form toxic and allergenic chloride complexes in the respiratory tract.[25a] Platinum, palladium, and rhodium were found to either accumulate in the liver and kidney after ingestion, or in the lungs, kidneys, and bones after inhalation. After intravenous injection, platinum and palladium also accumulated in the spleen, lungs, and bones, and rhodium in the muscles and bones.[17a] The major elimination ways of these metals seem to be by urine and feces.[17a,46,91,119]

Palladium is characterized by the highest bioavailability among the platinum-group metals.[11b,e] Retention of palladium in the body was shown to depend on the way by which it is administered. In rats, oral administration of $PdCl_2$ resulted in almost complete three-day elimination, whereas intratracheal or intravenous administration led to prolonged retention of palladium in the body. Absorption of palladium through the digestive tract was shown to be insignificant. Although acute toxicity of palladium compounds is low, they may cause kidney and lung damage.[17a,46,91,119] Palladium also demonstrated sensitizing activity, showed specific cross-sensitization with nickel and was able to penetrate through the skin.[100,114,118–120]

Pd^{2+} ions were slowly taken up by murine cells and distributed to the nucleus and mitochondria. There was a report on Pd^{2+} replacing Fe^{2+} in the active center of the enzyme prolyl hydroxylase.[119a] Pd^{2+} also inhibited other enzymes, such as aldolase, carbonic anhydrase, succinic dehydrogenase, alkaline phosphatase, and acetylcholinesterase. Moreover, palladium suppressed the addition of thymine to DNA in the liver, spleen, and testicles.[91] $PdCl_2$ interacted with DNA, mostly through noncovalent binding, and induced its conformational changes and cleavage. Palladium compounds were shown to influence the levels of prostaglandins and interleukins.[11c] Palladium treatment resulted in pericardiac edema in zebrafish embryos.[11e]

Workers of plants involved in manufacture and recycling of automobile catalytic converters suffer from occupational asthma and platinosis provoked by chloroplatinates.[100] The allergic potential of platinum salts is thought to increase with the increasing number of chlorine atoms, whereas nonhalogenated and neutral compounds are suggested to be nonallergenic.[118a] Occupational allergy to platinum was reported.[91,114]

Platinum is an essential component of several chemotherapeutic drugs, the most common of which is *cis*-diamminedichloroplatinum(II) [*cis*-$Pt(NH_3)_2Cl_2$; cisplatin]. These drugs are complexes of platinum(II) with two inert and two labile ligands.[10h,121] The mechanism of cisplatin action has been studied in detail: after entering the cell by cation transporters, cisplatin undergoes ligand substitution, binds to available DNA (preferably at guanine residues exposed in the major grove) and crosslinks it. The corresponding DNA damage induces cell-cycle arrest followed by apoptosis.[121] Apparently, only platinum compounds of certain type cause profound toxic effects, as $PtCl_2$ demonstrates low toxicity and $PtCl_4$ is significantly more toxic (Table 2). Both cisplatin and $PtCl_4$ demonstrate mutagenic activity.[17a] Pt^{2+} and Pt^{4+} compounds may increase production of ROS and may bind to different proteins possibly interfering with their activity. Pt^{4+} was shown to oxidize sulfur-containing side chains of amino acids.[91]

Treatment with platinum-based drugs results in prolonged elevated levels of platinum in the liver[17a,46,91,119a] and often produces adverse side effects, including nephrotoxicity.[118a] Four-week exposure to platinum salts per gavage led to DNA damage and kidney alterations in rats,[122] whereas four-week intraperitoneal injection of platinum subnanoparticles (<1 nm) caused nephrotoxicity in mice. However, 8 nm particles produced no adverse effect.[62b] Interestingly, pretreatment with low doses of $PtCl_4$ demonstrated a protective effect against lethality to higher doses in rats.[47b]

There are almost no data on chronic toxicity of rhodium compounds. Absorption of rhodium by the human organism is supposed to be low. In case of inhalation, rhodium compounds

may form rhodium chloride complexes in the airways. Soluble salts of rhodium were shown to cause eye irritation, whereas rhodium(I) acetylacetonate produced allergic reaction in guinea pigs.[91] In several cases of occupational exposure, sensitizing activity of rhodium was observed in humans.[123]

Rhodium compounds, especially those containing rhodium(III), are genotoxic and mutagenic in bacteria.[124] Rhodium complexes, particularly those with rhodium(I), rhodium(II), and rhodium(III), are being studied as potential anticancer drugs.[10e] They inhibited DNA synthesis and influenced the immune response in mice.[125] Several rhodium complexes were shown to bind DNA.[126] The potential antitumor agent rhodium(II) citrate manifested no apparent subchonic toxicity in mice.[127]

8. Summary and Outlook

In summary, an assumption of toxic heavy metals and benign lighter metals should not be taken for granted. The essential trace nutrients nickel and copper may be as toxic (or significantly more toxic) as the traditionally poisonous platinum, palladium, and rhodium. Another important point is that the toxicity of a given metal is not constant and depends on its bioavailability, solubility, valence state, particle size, the nature of coordinated ligands, etc.

Therefore, when assessing the toxic effects of metal salts, we may face the issue of mismatching and even inconsistent data. Parting this veil may change our traditional views on benign and dangerous substances. To rely on these data and to use them in the development and application of chemicals, we need not only to conduct more detailed and accurate toxicological measurements, but also to know why the toxic effects arise and how they are influenced by the nature of metal complexes and the ligand environment.

From the point of view of available toxicity data, light metals do not always have obvious advantages compared to heavy ones. Therefore, the development of transition-metal catalysts using light and heavy metals can be considered equally important areas, where the toxicity assessment should not rely on common assumptions. Dedicated measurements should be performed for particular complexes of interest, and the nature, oxidation state, and ligands of a metal, as well as possible exposure routes and bioavailability, should be taken into account. At the moment, the available data are insufficient for using a general toxicity term as a key characteristic when designing new catalysts. Without targeted assessment of biological activity, toxicity/nontoxicity speculations should not be employed as a sole "selling point" of a new catalytic system.

The lower price of iron, nickel, and copper is an important factor from the point of view of the sustainable development. However, careful consideration of the environmental impact is a key question, and the complete life cycle of a chemical process should be considered. Usage of inexpensive catalysts may be accompanied by subsequent utilization of toxic wastes, thus affecting the overall cost-efficiency considerably.

Essential trace elements, such as nickel, copper, and iron, are frequently thought to be less toxic, than palladium, platinum, and gold. However, both copper and iron initiate Fenton-type reactions leading to the generation of highly reactive hydroxyl radicals, which damage proteins, lipids, and DNA within living cells, whereas nickel compounds are well-recognized carcinogens. Nevertheless, the purpose of this review is not to claim the safety of palladium, platinum, rhodium, and gold, since these metals also have significant biological impacts.

In spite of several studies, the exact molecular mechanisms which underlie the toxic effects of metal compounds have not been completely elucidated so far, and the full picture is yet to be revealed. We cannot define the precise order of relative toxicities of the metal compounds based on the available data, and only estimations can be made. In many cases, the published data report rather different toxicity values without discussing the origin of the difference. Often, measurements of biological activity provide no clear description of concentrations and composition of metal salts used in the study, thus hindering the direct comparison of toxicity values obtained in different publications. Available literature data on metal species are somewhat vague and controversial. Obviously, more accurate and detailed studies are required to reveal the environmental and biological impact of metal compounds.

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