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The evaluation of potential toxic metal levels of various drugs used in children

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ABSTRACT

Aims: Medicines have been widely used in recent years to support the immune system. Exposure to toxic metals can occur at different stages, such as raw material procurement, production, and packaging of drugs designed to support the immune system. This exposure can lead to serious health problems. In this study, the aim was to determine the levels of toxic metals in drugs used to support the immune system in children.

Methods: Ten drug samples, available in pharmacies and intended for strengthening the immune system in children, were collected. Preliminary processes were conducted for the ICP-MS analysis of these collected drugs. Following the initial preparation, levels of Arsenic (As), Copper (Cu), Zinc (Zn), Manganese (Mn), Selenium (Se), Chromium (Cr), Mercury (Hg), Lead (Pb), Cadmium (Cd), Tin (Sn), Cobalt (Co), Aluminum (Al), Molybdenum (Mo), Antimony (Sb), Nickel (Ni) were determined using an ICP-MS device.

Results: In our study, we evaluated the levels of toxic metals in drugs used to support the immune system. The average levels of Cr, Zn, As, Se, Cd, and Sn in the samples were found to exceed the limits set by international organizations. However, the average levels of Al, Cu, and Hg were very close to these limit levels. On the other hand, the levels of Mo, Sb, and Pb in the analyzed products were well below the established limits.

Conclusion: The levels of toxic metals in immune-supporting drugs can lead to toxicity when the results of the study are evaluated. To inform consumers and safeguard their health, it would be appropriate for manufacturers to include information about the daily intake limits set by international organizations for toxic metals and trace elements. Conducting toxicological tests, especially during these inspections, will greatly contribute to protecting the health of children and fostering the development of healthy generations.

Keywords: Drug, child, toxic metals, immune system

INTRODUCTION

To support the immune system, it is used in immune-supportive drugs and food supplements. The licensing process for food supplements is carried out by the Ministry of Agriculture and Forestry.[1] As with other drugs, the licensing process for drugs that support the immune system is carried out by the Turkish Medicines and Medical Devices Agency. The legal definition has been established as follows: "Pharmaceutical product for human use (medicine): A substance or combination of substances that are presented as having therapeutic or preventive properties for human disease, or that are used or administered to humans for the purpose of correcting, improving, or changing physiological functions or medical diagnosis by showing pharmacological, immunological, or metabolic effects".[2]

For a product to be licensed as a drug, it must pass numerous tests. Additionally, advertising of a drug-licensed product is prohibited.[3] From this perspective, it is quite natural that food supplements, licensed as immune system supporters and easily advertised, are widely used by society. However, the use of drugs that support the immune system by physicians for pediatric patients is also quite high. In the USA, 60% of the public uses the 55,000 immune system supplements available in the market. About 50% of people in Europe and 71% in Canada use natural herbal products.[4–6] In another study, it was reported that children constituted 9% of the immune system supporters consumed in the United States. About one-third of infants, children, and adolescents in the United States use immunosuppressants.[7,8] It consists

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of vitamins and vitamin-mineral complexes, and it is among the most commonly used immune system supporters in Turkiye.[9] Immune system boosters are products marketed to protect or improve health, and they can also be used to reduce disease symptoms or treat diseases.[10] However, numerous studies demonstrate that immunosuppressants can lead to both acute and chronic toxicity.[11] Cases of poisoning with toxic metals found in medicinal plants used as immune system boosters have been reported in the USA, Europe, and Asia.[12–15]

In fact, some of the metals evaluated are essential for the body and are included in products that support the immune system. However, these metals are assessed due to the potential harm caused by their high levels. ATSDR, a federal public health agency under the U.S. Department of Health and Human Services, aims to protect the public from health problems that may arise from exposure to natural and man-made hazardous materials. Additionally, ATSDR conducts research on the health effects of hazardous waste sites and provides actionable guidance to address environmental health threats.[16] USP is an independent, scientific, non-profit organization focused on building trust in the supply of safe and quality medicines. It was established to strengthen the global supply chain, ensuring that medicines, which people trust for their health, are ready when needed and working as expected.[17] The Turkish Food Codex has been prepared by the Ministry of Agriculture and Forestry to ensure consumer and human health, protect consumer rights, ensure justice in food sales, and promote environmental protection where appropriate.[18]

The increasing environmental pollution resulting from industrialization and urbanization, along with soil pollution, has reached levels that can pose a danger to living things. Environmental and soil pollution can cause contamination in food sources through the food chain. This situation has the potential to create significant health problems for people.[19]

One of the most significant threats to human health is toxic metals.[19] oxic metals can enter the human body through various pathways, including food, respiratory exposure, or skin contact. They are known to cause adverse health effects and, in severe cases, can lead to death.[20] It is observed that human activities have a more significant impact than natural cycles in the spread of toxic metals into the environment. These metals, transmitted to the environment in various ways, can further spread to grains, animals fed with contaminated grass, milk and meat, fish caught from polluted waters, or tools and equipment used during food production.[19] With the increase in industrialization, the risk of drug contamination with toxic metals is rising day by day.

Due to the COVID-19 pandemic, drugs with antimicrobial and immunomodulatory activities are considered promising therapeutic support for preventing viral spread. This has led to physicians prescribing these drugs, which are frequently used by parents to protect the health of their children.[21] There is a possibility that our children may experience health problems due to the presence of toxic metals in immunosuppressive drugs used to protect their health. This situation emerges as a significant problem that can threaten public health.

This study was conducted to determine the levels of toxic metals, which can pose serious threats to human health, especially in drugs used to support the immune system in children. The aim is to provide information about the residue status of these drugs.

METHODS

Supply of Immune System-Supporting Drugs

Immune system-supporting drugs from commercial companies were obtained from pharmacies in Yozgat. These products were numbered, and subsequent analysis and evaluation processes were conducted based on these numbers. Our study did not receive ethical committee approval since it does not fall within the scope of "Regulation on Clinical Research of Medicinal and Biological Products," "Guideline on Good Clinical Practice," and "Yozgat Bozok University Clinical Research Ethics Committee Regulation."

Preliminary Preparation of Samples

The preliminary preparation of the samples was carried out by the method developed by Türksoy et al.[22] in the Yozgat Bozok University Faculty of Medicine Research Laboratory. The samples were dried in a polystyrene petri dish in an incubator at 75°C for 24 hours. The samples collected from the incubator were weighed to determine the amount of dry matter. Afterwards, the samples were placed in 50 ml polypropylene tubes. The preparation of samples was performed by treating the samples with 2 ml of hydrogen peroxide (H_2O_2) and 7 ml of suprapur nitric acid (HNO_3). The prepared samples were filtered and taken into 15 ml polypropylene tubes for analysis by inductively coupled plasma mass spectrometry (ICP-MS). The prepared samples were stored at 4°C until the date of ICP-MS analysis.[22]

Determination of Toxic Metal Levels in Drugs Used to Support The Immune System With ICP-MS

ICP-MS (Thermo Scientific, ICAPQc, USA) system was used to determine the levels of Arsenic (As), copper (Cu), zinc (Zn), manganese (Mn), selenium (Se), chromium (Cr), mercury (Hg), lead (Pb), cadmium (Cd), tin (Sn), cobalt (Co), aluminum (Al), molybdenum

(Mo), antimony (Sb), nickel (Ni) in the samples. For this, the method developed by Türksoy et al.[22] was used. The operating parameters were set as follows: RF power 1550 W, nebulizer gas flow 0.90 L,/min, nebulizer pressure 3.08 bar, plasma gas flow 0.80 L/min, dwell tie 0.01, spray chamber temperature 3.01. The probe of sampler was washed between injections for rinsing. Rinsing of the probe firstly washed 30s with ultrapure water, then 45s with 2% HNO_3 , followed by washing 45s with ultrapure water. A total of 11 point calibration curves (quanitative mode linear calibration; R^2>0.99 with interval of calibration 0.5-1000 µg/g) were drawn for each toxic metal and the results were evaluated according to these calibration curves.

Statistical Analysis

Data analysis was performed using the IBM SPSS 23.0 package program. Parametric tests were used for ordered data and non-parametric tests were used for non-ordered data. Descriptive statistics were shown with mean, standard error, and minimum-maximum values. Evaluation of data in terms of toxicity was done with reference values of Turkish Food Codex Contaminants Regulation, Agency for toxic substances and disease registry (ATSDR) and United States Pharmacopeia (USP).[16,17,23] The Kolmogorov-Smirnov test was used to determine whether the data were distributed normally. Spearman Correlation Analysis was applied in order to determine the relationship between the data. p<0.05 was considered significant.

RESULTS

In our study, we evaluated the toxic metal levels in 10 drugs used to support the immune system. Arsenic (As) was detected at 0.237 µg/g in one of our samples, with a mean level of 0.053 µg/g. The levels of Chromium (Cr) and Cobalt (Co) exceeded the daily intake limits determined by ATSDR in 10% of the samples, while Mercury (Hg) exceeded the limit in 20%. Zinc (Zn), Arsenic (As), Selenium (Se), and Cadmium (Cd) exceeded the daily intake limits in 100% of the samples in our study.[16] The toxic metal levels detected in the immune system-supporting drugs, the daily allowable intake limits accepted by various organizations, and the maximum toxic metal levels that should be found in immune system supporters are presented in **Table 1**.

The levels of toxic metals detected as a result of the analysis of drugs used to support the immune system are given in **Figure 1**.

Table 1. Toxic metal levels in drugs used to support the immune system

	N	Mean (µg/g)	Standard error	Minimum	Maximum	Daily allowable limits (µg/day)	Accepted limits µg/g
Al	10	0.037	0.042	0.001	0.119	1λ	
Cr	10	0.004	0.002	0.003	0.009	0.0005λ 150*	
Mn	10	0.189	0.155	0.126	0.630		1500**
Co	10	0.014	0.008	0.009	0.035	0.03λ	
Ni	10	0.002	0.002	0.002	0.007		
Cu	10	0.010	0.004	0.007	0.018	0.02λ 1000* 300†	100**
Zn	10	0.626	0.192	0.377	1.04	0.3λ 15000* 6000†	1500**
As	10	0.053	0.067	0.007	0.237	0.005λ 1.5* 10†	0.020* 0.15**
Se	10	0.041	0.028	0.021	0.110	0.005λ 250*	25**
Mo	10	0.003	0.003	0.002	0.011	0.06λ 100*	10**
Cd	10	0.005	0.004	0.004	0.016	0.0005λ 25* 6†	1* 2.5**
Sn	10	0.003	0.002	0.001	0.006	0.0003λ	50*
Sb	10	0.001	0.0004	0.001	0.002	1λ	
Hg	10	0.001	0.001	0.0004	0.003	0.002λ 15* 3.42†	0.10* 1.5**
Pb	10	0.034	0.030	0.002	0.073	5* 21.4†	3* 0.5**

* Turkish Food Codex Contaminants Regulation.[47]
** Maximum metal levels accepted in Tablets according to the US Pharmacopoeia (USP) (µg/g).[48]
⁕ Allowable daily exposure according to the US Pharmacopeia (USP) (µg/day).[48]
† WHO/FAO: Allowed daily intake calculated using 10% for 60 kg body weight and dietary supplements (µg/day).[48]
λ ATSDR (minimal risk seviyesi) göre izin verilen günlük maruziyet miktarı (µg/g /day).[49]

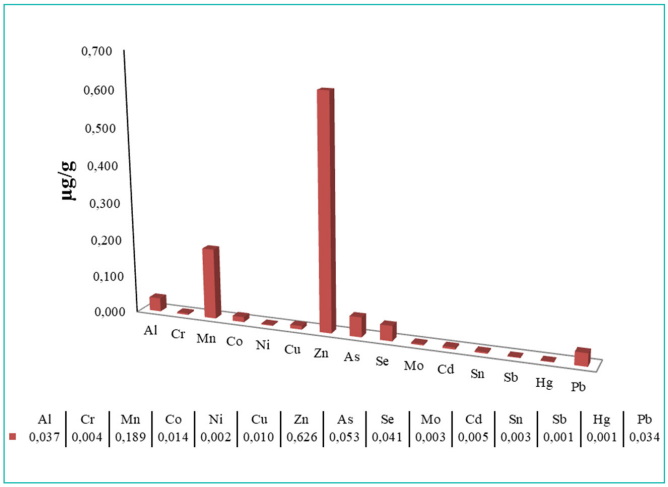

Figure 1. Toxic metal levels in immune system supplements sold as drugs

As a result of our study, the mean and standard error values of the Al, Cr, Sn, Co, Zn, Mn, Cu and Se levels detected in the drugs used to support the immune system, together with the values determined to be more or less than the mean values, are given in Figure 2. Excess values of these metals were detected in 1 sample each for Co, Mn and Cu, and 2 samples each for Cr and Se in the studied immune system supporters.

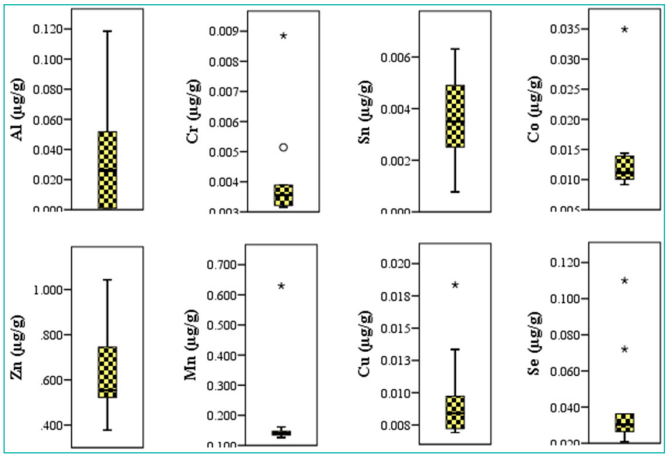

Figure 2. Aluminum (Al), Chromium (Cr), Tin (Sn), Cobalt (Co), Zinc (Zn), Manganese (Mn), Copper (Cu) and Selenium (Se) values in immune system supporting products sold as drugs . "*" and "o" indicate extremely high values and "⊤" indicates standard error. "▩" indicates immune system boosters sold as drugs.

The mean and standard error values of As, Cd, Hg, Pb, Sb, Mo and Ni levels detected in drugs used to support the immune system, as well as values that were determined to be more or less than the mean values are given in Figure 3. Levels of 1 each for As, Cd, Sb, Mo and Ni and 2 samples for Hg were well above the average values.

It was determined that the limit set by ATSDR was exceeded in 10 samples for Zn, Se, Cd, and As, 2 samples for Hg, and 1 sample for Cr and Co samples exceeding the limits set for Zn, Se, Cr, Cd, As, Hg and Co are given in Figure 4.

The differences between toxic metal levels from immune system boosters are described in Table 2. The positive correlations were found between Cr and Mn, Co, Cu, Se, and negative correlation was found between Cr and Pb (respectively; r=0.721; r=0.697; r=0.648; r=0.661; r=-0.661; p<0.01). On the other hand positive correlations were found with Mn and Se, Mn and Mo, Co and Ni, Co and Hg (respectively; r=0.867; r=0.733; r=0.794; p<0.01; r=0.648; p<0.05). However a positive correlation was too detected between Ni and Sn, Ni and Hg, Mo and Cd (respectively; r=0.721; r=0.661; r=0.733; p<0.05).

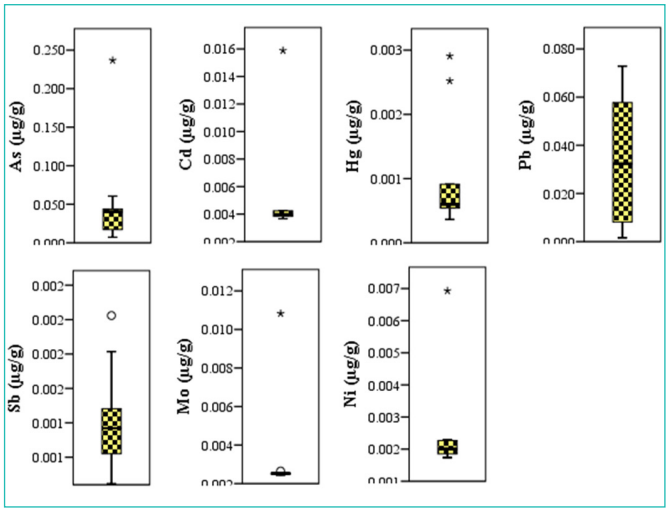

Figure 3. Arsenic (As), Cadmium (Cd), Mercury (Hg), Lead (Pb), Antimony (Sb), Molybdenum (Mo) and Nickel (Ni) values in immune system support products sold as drugs. "*" and "o" indicate extremely high values and "⊤" indicates standard error. "▩" indicates immune system boosters sold as drugs.

Figure 4. Samples exceeding the specified limit for Zinc (Zn), Selenium (Se), Chromium (Cr), Cobalt (Co), Mercury (Hg), Cadmium (Cd) and Arsenic (As). Limit: Allowed daily exposure amount (µg/g/day) according to minimal risk level of ATSDR

Table 2. Relationship between toxic metals in immune system supplements sold as drugs

	Cr (µg/L)	Mn (µg/L)	Co (µg/L)	Ni (µg/L)	Cu (µg/L)	Zn (µg/L)	As (µg/L)	Se (µg/L)	Mo (µg/L)	Cd (µg/L)	Sn (µg/L)	Sb (µg/L)	Hg (µg/L)	Pb (µg/L)
Al (µg/L)	-0.129	-0.276	0.104	0.276	-0.399	-0.62	-0.534	0.031	-0.08	-0.264	-0.043	0.092	-0.252	-0.141
Cr (µg/L)	1.000	0.721*	0.697*	0.37	0.648*	0.103	0.03	0.661*	0.358	0.212	0.127	-0.358	0.406	-0.661*
Mn (µg/L)		1.000	0.467	0.224	0.43	0.248	-0.018	0.867**	0.733*	0.43	-0.152	-0.442	0.406	-0.539
Co (µg/L)			1.000	0.794**	0.515	-0.067	-0.03	0.6	0.103	-0.285	0.564	-0.115	0.648*	-0.261
Ni (µg/L)				1.000	0.406	0.018	0.127	0.515	0.03	-0.188	0.721*	-0.03	0.661*	0.042
Cu (µg/L)					1.000	0.503	0.103	0.515	-0.103	0.103	0.394	-0.394	0.37	0.018
Zn (µg/L)						1.000	0.345	0.273	0.224	0.442	-0.091	-0.261	-0.006	0.091
As (µg/L)							1.000	-0.079	0.091	0.285	0.442	-0.236	0.188	0.273
Se (µg/L)								1.000	0.6	0.309	0.042	-0.588	0.297	-0.345
Mo (µg/L)									1.000	0.733*	-0.479	-0.382	0.103	-0.612
Cd (µg/L)										1.000	-0.479	-0.515	-0.127	-0.345
Sn (µg/L)											1.000	0.055	0.576	0.491
Sb (µg/L)												1.000	0.309	-0.018
Hg (µg/L)													1.000	-0.103

DISCUSSION

In this study, we evaluated the immune-supporting drugs that are most commonly used in the market. Drugs containing toxic metals, organic solvents, and various toxins can cause damage to many systems, especially the nervous system.[24] When the level of heavy metals in our body exceeds permissible limits, it can lead to serious health problems. Elevated levels of heavy metals such as Pb, Cr, As, Hg, Ni, and Cd beyond the permissible limits can cause hepatotoxicity.[25] In their study (Gravey et al.[11]), stated that there are toxic metals in medicinal plants used as immune system supporters and this will adversely affect people's health. In another study (Dunbabin et al.[14]), reported that lead poisoning occurred due to Indian herbal medicines used as immune system supporters.

In our study, the mean value of As in the samples was determined to be 0.053 µg/g, which significantly exceeded the level accepted in the Turkish Food Codex Contaminants Regulation of 0.020 µg/g.[18] However, the As level detected in all samples exceeded the limits set by the ATSDR.[16] In a study of acute As poisoning in swine, symptoms such as vomiting, diarrhea, colic, dehydration, collapse, convulsions, and death were observed within a time period ranging from hours to days. This study revealed a one-tenth difference between the administered dose and the concentration of As in liver and kidney tissue.[26]

Cadmium is a heavy metal that lacks physiological function and is generally considered toxic. The biological half-life of Cd in humans is approximately 20-30 years. Cd exhibits various toxic effects, including nephrotoxicity, carcinogenicity, teratogenicity, as well as endocrine and reproductive toxicities. At the cellular level, cadmium influences cell proliferation, differentiation, apoptosis, and other cellular activities.[27] One of the negative effects of Cd exposure in children is osteoporosis. Due to the limited excretion of Cd, children may experience the accumulation of this metal in their bodies. Afterward, osteoporosis and an increased risk of fractures emerge when the child becomes an adult.[28] Sherief et al.[29] associated Cd exposure with pediatric cancer in their study. When cadmium levels in nails, hair, urine and serum of cancer patients and healthy people were measured by Atomic Using an Absorption Spectrophotometer, it was determined that children with cancer had higher cadmium levels than children without cancer. In our study, it was found that the level of Cd exceeded the limit set by ATSDR in all samples. When the results of our study and the existing literature are evaluated together, it suggests that parents using immune system supporters to protect their children's health may inadvertently expose them to the risk of osteoporosis and even cancer.

Hg is a toxic heavy metal commonly found in nature. It provides no physiological benefit to either children or adults. Hg has teratogenic, carcinogenic, and mutagenic effects, as well as cardio-, nephro-, and immunotoxicity.[30] Hg accumulates in various parts of the human body; therefore, the range of symptoms caused by Hg is quite wide. These symptoms include fatigue, anxiety, depression, paresthesias, weight loss, memory loss, and difficulty concentrating.[31] Prenatal Hg exposure is associated with decreased IQ scores and impaired performance on tests of memory, attention, language, and spatial cognition.[30] In a study conducted in the USA, it was stated that industrial Hg exposure decreased the IQs of 300.000-600.000 US children.[32] In our study, the sample rate above the limit value set by ATSDR for Hg was determined as 20%. Considering the mutagenic and carcinogenic effects observed in children after Hg exposure, it can be concluded that the use of immune system supporters may potentially lead to such toxic symptoms in children in the future.

Pb enters the human body through the food chain, including food and water. It accumulates in the kidneys, liver, brain, bones, and other organs.[33] Oxidative stress and inflammation occurring after Pb exposure can cause cell damage.[34,35] Pb exposure increases the risk of developing neurodegenerative diseases especially in childhood.[36] The Scientific Committee on Neurotoxicology and Psychophysiology and The Scientific Committee on The Toxicology of Metals of The International Commission on Occupational Health in 2006 recommended that blood lead level should be below 5 µg/dl in children.[37] In our study, the Pb value was well below the level accepted in the Turkish Food Codex Contaminants Regulation, at 3 µg/g.

Although Cr is an essential metal for the human body, it is also recognized as a potent human carcinogen by the International Agency for Research on Cancer (IARC). There are epidemiological studies of Cr-induced cancer development among industrially exposed workers.38 In one of the samples in our study, Cr values were found above the limit set by ATSDR. This situation can be considered as an indication that those who use these products to support the immune system may face cancer risk in the future.

Se is an essential trace element with both beneficial and adverse health consequences as a component of major metabolic pathways, including the antioxidant defense system, DNA synthesis, and immunological functions. Se deficiency has been associated with many diseases such as cancer, immune deficiency, hormone synthesis disorders, and neurodegenerative diseases including Alzheimer's and Parkinson's disease.[39–42] However, selenium is toxic in high concentration. Se toxicity can be classified to acute or chronic. Acute poisoning typically involves a single dose that produces symptoms within minutes, while chronic poisoning involves smaller doses given repeatedly that produce symptoms that become evident within days or longer.[43] In a study, Gardiner stated that chronic Se exposure causes Se accumulation in the liver and kidneys of sheep, and as a result of the 72-week study, 5 out of 9 sheep died.[44] The Se level detected in all of the samples was determined above the limit set by ATSDR.

Zn is an essential trace element that the body uses in many ways. Zn functions as a component of 200-300 enzymes to assist the most important metabolic pathways in the body responsible for structural, catalytic and biochemical functions. It is also thought to have an important role in cell proliferation in the body and in Zn hemostasis of the thyroid·45 Zn is included in the composition of many immune-supporting drugs and food supplements. Zn toxicity has been rarely reported in childhood. As a result of excessive Zn intake, nausea, vomiting, loss of appetite, diarrhea and headache may occur.[46] In our study, it was determined that the limit value set by ATSDR for Zn was exceeded in all of the samples.

CONCLUSION

The aim of our study is to unveil the status of toxic metal levels in immune-supporting drugs, the usage of which has increased in recent years, particularly with the pandemic. It's important to note that our goal is not to disparage immune system-supporting drugs or the industry. Our findings indicate that those who use these products for health protection may be exposed to varying levels of toxic metals, as we have detected certain rates of these metals and trace elements that can lead to toxicity if consumed excessively. To inform consumers, we suggest that manufacturers consider adding the daily intake limits set by international organizations for metals and the metal levels in their products to product labels (prospectus). However, we emphasize the need for more effective legal regulation and supervision in the supply of raw materials, production, and marketing of immune system-supportive drugs. This approach is essential to prevent potential harm to individuals who use these products for health protection. Conducting toxicological tests, especially during these inspections, will significantly contribute to safeguarding the health of children and fostering the development of healthy generations

ETHICAL DECLARATIONS

Ethics Committee Approval

Ethics committee approval is not required for this study.

Informed Consent

Informed Consent is not required for this study.

Referee Evaluation Process

Externally peer reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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