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REVIEW RHEUMATOLOGY

Toxic metals in rheumatological diseases: A systematic review

Jozélio Freire de Carvalho,[1] Thelma L Skare[2]

[1]Research Center for Chronic Non-Communicable Diseases (NUPEC), School of Nutrition, Federal University of Bahia, Salvador, Brazil
[2]Department of Rheumatology, Mackenzie Evangelical University Hospital, Curitiba, Brazil

ABSTRACT

Heavy metals exposure might be linked to rheumatic diseases and has been studied in a few articles. The aim of this article is to review the studies that evaluated metal toxicity in rheumatological diseases. A systematic search of PubMed, Embase, and Scielo databases was performed, looking for articles on toxic metals and rheumatic diseases published between 1966 and March 2023. A total of 31 studies (1,559 RA and 4,308 patients with other rheumatic diseases) were included. Most patients were females, ranging from 4 to 62 years old. Although most studies showed higher concentrations of toxic metals in rheumatic diseases, a few showed a positive association with disease activity or severity of the conditions. This systematic review reveals the presence of toxic metals in patients with rheumatic disease. Screening for toxic metals may be elucidative in selected cases.

Keywords: Metal toxicity; metals; rheumatic diseases; rheumatoid arthritis.

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The frequency of rheumatic diseases ranges from rare conditions such as primary vasculitis to very prevalent disorders, including fibromyalgia, which affects 5% of the population, and osteoarthritis, which involves 60% of the old population at 70 years old [1].

The causes of rheumatic disorders are not entirely known, but genetic and environmental factors are considered critical factors in these disorders. Concerning genetic factors, HLA-DR4, PTPN22, and HLA-B27 are widely known to predispose patients to autoimmunity [1]. On the other hand, environmental factors are related to hormones, ultraviolet radiation, medication use (e.g., estrogen, procainamide, hydralazine, etc.), vaccines, and metals. In this context, some studies reported that mercury and gold may induce autoimmunity in animal models [1]; there is evidence of the interplay of toxic metals in the pathophysiology of rheumatic diseases [2].

The purpose of this study is to provide a systematic review of studies assessing metal toxicity in rheumatic diseases.

METHODS

Literature Review

We systematically searched the papers published from 1966 to March 2023 in PubMed/MEDLINE, EMBASE, and Scielo utilizing these MeSH entry terms: "metal toxicity" OR " metal poisoning" OR "metal intoxication" OR "trace element" AND "rheumatic" OR "rheumatologic" OR "fibromyalgia" OR "rheumatoid arthritis" OR "spondyloarthritis" OR "Sjögren's syndrome" OR "myositis" OR "systemic sclerosis" OR "osteoarthritis" OR "gout" OR "antiphospholipid syndrome" OR "gout" OR "osteoarthritis" OR "spondyloarthritis" OR "ankylos-

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Correspondence: Jozélio Freire de CARVALHO, MD. Research Center for Chronic Non-Communicable Diseases (NUPEC), School of Nutrition, Federal University of Bahia, Salvador, Brazil.
Tel: +5571-99187-1169 e-mail: jotafc@gmail.com

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ing spondylitis" OR "psoriatic arthritis" OR "vasculitis" OR "Behçet's disease" OR "familial Mediterranean fever". In other datasets, we used similar techniques. No language restrictions were present in any associated articles. The chosen articles' reference lists were examined to find other works. Initially, the literature search and research abstract selection were carried out independently by JFC and TLS. The full-text articles chosen by abstracts were reviewed separately by the same reviewers in the second step. At consensus meetings, conflicts were settled by a third reviewer. The writers adhered to PRISMA standards [3]. The authors, year of publication, number of patients investigated, demographic information, duration of the ailment, toxic metal specification, results, and effects were all extracted from the studies using a standardized manner. Evaluations of hazardous metals, rheumatic disorders, and clinical trials were required for inclusion. Articles involving animal experiments, review papers, and in vitro research were excluded.

RESULTS

Appendix 1 summarizes the studies in which toxic metals were evaluated in RA [4–11]. These articles came from Pakistan (n=2), Denmark (n=1), Iraq (n=1), Italy (n=1), Korea (n=1), Taiwan (n=1), and the United States (n=1). Study design, most of them were cross-sectional (n=6) [4–9], case-control (n=1) [10], and case report (n=1) [11]. A total of 8 studies with 1,559 RA patients were evaluated. Age varied from 20 to 62 years old, and female gender from 44% [9] to 100% [5]. In summary, all studies demonstrated increased levels of toxic metals in R.A. subjects, including Cd (n=5), Cu (n=1), Ni (n=2), Pb (n=3), As (n=1), and Hb (n=1).

Appendix 2 shows 22 articles that evaluated toxic metals in other rheumatic diseases [12–34], including SLE (n=5) [12–16], gout or hyperuricemia (n=4) [17–20], systemic sclerosis (n=3) [21–23], miners (n=2) [24, 25], fibromyalgia (n=1) [26], rheumatic fever (n=1) [27], polyarteritis nodosa (n=1) [28], more than one disease studied (n=4) [29–32], unspecified arthritis (n=1) [33] and granulomatosis with polyangiitis (n=1) [34]. Brazil (n=3), Czechia (n=1), Canada (n=1), Italy (n=1), Norway (n=2), France (n=1), Turkiye (n=1), the UK (n=1), the USA (n=5), New Zealand (n=1), and Switzerland (n=1) were the nations that generated the articles. Concerning study design, most of them were cross-sectional (n=14) [12, 13, 17, 19–21, 23–25, 27, 29–31, 33], followed by case report (n=3) [14, 16, 28], prospective (n=2) [15, 26], case series (n=1) [32], case-control (n=2) [22, 34]. A total of 7,883 participants, including 4,259 patients with gout [17–20], 174 lupus [12–14], 179 systemic sclerosis [21–23], 617 miners [24, 25], 33 rheumatic fever [27], 1 polyarteritis nodosa [28], 1 granulomatosis with polyangiitis [34], 39 pediatric rheumatic diseases [14, 27, 32], and 2,546 with two or more conditions [29–32]. Age varied from 4 [32] to 64.7 [19] years old, and female gender from 0 [18] to 96.2% [13]. Disease duration ranged from 2 weeks [32] to 33 years [28].

Regarding lupus studies, low levels of lead were observed in one study, although high lead levels were associated with lupus diagnosis [12]. In the other study, mercury levels were negatively linked to disease activity measured by BILAG and SLICC [13]. The other 2 studies were case reports showing lupus-like induced by toxic metals [13, 14]. The gout studies showed an association of this metabolic disorder with mercury and lead. SSc was associated with increased levels of several toxic metals [21–23]. The authors reported that mercury exposure was linked to positive ANA, anti-nucleolar, and other autoantibodies directed against GSTA1, TNF ligand superfamily member 13, and others [24, 25]. The authors of the fibromyalgia paper discovered that all patients had at least one positive metal test; the most frequently positive were lead, nickel, inorganic mercury, and cadmium. No difference with healthy controls was detected in patients with acute rheumatic fever [27]. In one pediatrician study [32], the authors described 5 young relatives with clinical pictures of polyarteritis nodosa-like and erythromelalgia and were successfully treated with metal chelation. One study evaluated late hypersensitivity to heavy metals, not serum or hair metal levels [30].

Highlight key points

- Toxic metals are frequently detected at higher levels in patients with rheumatic diseases compared to healthy controls.
- Only a minority of studies link metal exposure directly to disease activity or severity.
- Mercury, lead, cadmium, and nickel are the most recurrent metals associated with autoimmune and inflammatory conditions.
- Metal exposure may mimic rheumatic symptoms, complicating diagnosis and clinical management.
- Screening for toxic metals could provide valuable insights in selected rheumatology cases.

DISCUSSION

This is the first study to systematically review all articles published on toxic metals in rheumatic diseases.

The human body requires certain trace elements (Cu, Zn, Mn among others) essential for human health. They are important because they form an essential part of enzymes involved in metabolic or biochemical processes. However, at high levels, these metals may become toxic, causing severe symptoms and even death. Harmful effects in most people result from years of accumulated exposure and storage in the body [29].

Heavy metal toxicity results from increasing pollution levels, industrial utilization, dental treatment, and exposure to jewelry use. They are present in soil, air, drinking water, cosmetics, medicines, fuel, etc. Dental restorations were connected to mercury, palladium, and gold exposure, while the patient's surroundings were linked to nickel and titanium exposure. The metal's distribution in the various target organs depends on the dose, route, and length of exposure [35–37].

Toxic metals alter the metabolism of metallothioneins and promote the synthesis of free radicals, increasing oxidative stress and causing depletion of the body's primary antioxidants. According to Lawrence et al. [38], toxic metals can damage mitochondrial DNA, resulting in mitochondrial dysfunction and oxidative stress. The depletion of glutathione and the amino acid cysteine, which is essential for glutathione synthesis, reduces the body's defenses against free radicals. Some of them, like Pb, negatively affect the metabolism of cytokines, including the interleukins IL-2, IL-1b, IL-8, IL-6, IL-4, tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN), as well as the expression and functioning of inflammatory enzymes such as cyclooxygenases [39]. It has also been proposed that exposure to certain toxic metals could disrupt the delicate balance between the immune and central nervous system [33]. It is interesting to note that the symptoms of metal toxicity, such as Pb and Al, include poor sleep, diffuse muscle pain, brain fog, chronic malaise, headaches, numbness, dizziness, and anxiety, which are the same as those of fibromyalgia [29].

Pathways that are toxic or allergic are crucial in metal pathology. Genetics may determine a person's susceptibility to metals and ability for detoxification. Additionally, it has been shown that smoking, which is linked to nickel sensitivity, is connected to SLE and R.A [7, 8]. Alcohol consumption may reduce the risk of arthritis at higher concentrations of Hg and Se [29]. Workplace co-exposure to mineral lubricants, silica, traffic pollution, and certain metals, including nickel, mercury, and palladium, are additional risk factors for connective tissue diseases. SLE has been observed to occur often in a population exposed to petroleum products and mercury [40]. A significant frequency of delayed-type metal hypersensitivity, notably to gold, titanium, nickel, palladium, mercury, or chromium, has also been shown to occur in SLE, Sjögren's syndrome, and R.A. patients. In people with metal sensitivities, reducing metal exposure may reduce inflammation and improve the effectiveness of conventional treatment [29].

Further research is needed on the role of metals in developing rheumatic illnesses and on potential immunotoxic processes; it is also unknown if metals interact with shielding micronutrients like vitamins and selenium.

The study's strengths include research with people who meet the worldwide criteria for rheumatic disorders and various study designs on toxic metals in rheumatic diseases. The authors assert that all documented instances of hazardous metal exposure in rheumatoid arthritis patients were gathered this way. However, some limitations were also observed. For example, no comparison between supplementation of micronutrients and classical treatments used in rheumatic diseases was available. Moreover, the number of participants in each study was small. In addition, a few rheumatic diseases were studied. Therefore, future studies, including larger patient samples, long-term follow-up, and diverse kinds of rheumatic disorders, are needed to understand the actual value of toxic metals in rheumatic diseases.

Conclusion

There are few studies in the literature evaluating the effects of toxic metals in rheumatological diseases, and only nine such conditions were addressed in this review.

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Appendix 1. Summary of the studies that evaluated toxic metals in rheumatoid arthritis

Author, reference	Study design	Country	n/gender	Age, years	Disease	Disease duration	Metal intoxication	Clinical and laboratory features
Khadim et al., 2023 [4]	Case-control	Iraq	120 R.A. and 60 HC 100% female.	20–60	R.A.	ND	Zn, Cu, Mg, Mn, Fe, Ni, Cr, K, Na, Ca, Pb, and Cd	In R.A. →Cu, Ni, Na, Pb, and Cd were high.
Joo et al., 2018. [5]	Cross-sectional study using Korean National Health and Nutrition Examination Survey (KNHANES) data	Korea	1,5559 R.A. from 53,829 subjects, 77% females	55.7	R.A.	ND	Cadmium, lead, mercury, zinc, and arsenicum were evaluated.	Cadmium was elevated in R.A. vs. control: 1.30±0.07 μg/L vs. 1.17±0.01 μg/L, p<0.01. No significant differences in urine levels of As or serum levels of Pb, Hg, Mn, or Zn
Yang et al., 2016 [6]	Cross-sectional	Taiwan	122 72% females	55.37± _ 13.51	R.A.	ND	Copper, Cr, As, Pb, Hg, Zn, Se.	R.A. patients living where farm soils contained high levels of copper had increased white blood cell counts, erythrocyte sedimentation rate, and disease activity score 28, compared with patients living where copper levels were low.
Afridi et al., 2015 [7]	Cross-sectional	Pakistan	53 49% females	42–56	R.A.	ND	Arsenic, cadmium mercury, and lead in blood and hair.	As Cd, Hg, and Pb were significantly higher in scalp hair and blood samples of R.A. than controls.
Afridi et al., 2011 [8]	Cross-sectional	Pakistan	53 49% females	42–56	R.A.	ND	Zn, Cu, Mn, Pb, and Cd were measured in scalp hair	Cd and Pb were significantly higher in scalp hair samples of R.A.
Bamonti et al., 2011. [9]	Case report	Italy	1 Female	63	R.A.	10 years	Aluminum, cadmium, and lead.	Lack of metacarpophalangeal joint range of motion and alignment. Increased CRP and ESR. She was treated with EDTA once a week for 1 year. the patient did not show any signs of mental intoxication. RA symptoms and oxidative status improved. After 6 months, methotrexate was reduced to 10 mg once every 10 days, and prednisolone to 5 mg/day.

Appendix 1 (cont). Summary of the studies that evaluated toxic metals in rheumatoid arthritis

Author, reference	Study design	Country	n/gender	Age, years	Disease	Disease duration	Metal intoxication	Clinical and laboratory features
Christensen et al., 1986 [10]	Cross-sectional	Denmark	10 vs. 10 HC	ND	R.A.	ND	Cr. Ni and Cd in blood, serum, urine, and sweat	Ni was higher in R.A. in the 3 fluids. Cr is higher in urine and lower in blood in R.A.
Niedermeyer et al., 1971 [11]	Cross-sectional	United States	44	45	R.A.	ND	Copper, iron, manganese, strontium, chromium, zinc, and molybdenum, Aluminum. barium, nickel, cesium, tin, lead and cadmium	In serum copper, barium, cesium, manganese, tin, and molybdenum were high; iron, zinc, and lead were low, and aluminum, nickel, strontium, chromium, and cadmium were normal. In joint fluid, the levels were normal.

ANA: Antinuclear antibodies; Cd: Cadmium; Cu: Copper; HC: Healthy controls; Mn: Manganese; RA: Rheumatoid arthritis; OA: Osteoarthritis; Pb: Lead; Zn: Zinc; ND: Not described; HC: Healthy controls.

Appendix 2. Summary of the studies that evaluated toxic metals in several rheumatic diseases

Author, reference	Study design	Country	n/gender	Age (years)	Disease	Disease duration	Metal intoxication	Clinical features
Pedro et al., 2017 [12]	Cross-sectional	Brazil	105 SLE and 120 HC 96% females	39.7 years	SLE	8 (3-15)	Li, V, Cu, Zn, Mo, Cd, and Pb in serum.	Lower V, Zn, and Pb, Mo, and Li in SLE. SLE diagnosis is associated with higher Li and lower V, Zn, and Pb. No association with disease activity.
Crowe et al., 2016 [13]	Cross-sectional	United Kingdom	52 96.2% females	48± 13.19	SLE	ND	Mercury in hair	Hair Hg, BILAG, and SLICC/ACR had a negative connection (r=_0.323, p=0.029 and r=_0.377, p=0.038, respectively). Hg in the urine did not correlate with disease activity or damage.
Kisaoglu et al., 2006 [14]	Case report	Turkiye	1 Female	13	SLE	1 month	Mercury	Myalgia, weight loss, hypertension, and proteinúria. Positive ANA, anti-dsDNA, and hypocomplementemia. SLE cured after treatment.
Prochazkova et al., 2004 [15]	Prospective	Czech Republic	15 66.7% females	36.5	SLE	13.3 months	Amalgama (inorganic mercury, silver, organic mercury, and lead)	10/15 improved, 4/15 unchanged, and 1 worsed objectively in the long-term.
Federmann et al., 1994 [16]	Case report	Switzerland	1 Female	24	SLE	ND	Lymphocyte transformation test (during prednisone at 10 mg/d) indicated a hypersensitivity to molybdenum	Clinical picture; fever, arthritis, oral ulcers, alopecia, pancytopenia, Coombs, anti-Ro/SS-A, anti-Sm, anti-RNP. and low complement levels.
Xu et al., 2022 [17]	Cross-sectional	United States	736 gout and 2,766 hyperuricemia from 14,871 50.7% females	50.02± 17.57	Gout and hyperuricemia	ND	Mercury	Mercury (quartile 2 and 4), lead (quartiles 2, 3, and 4), and selenium (quartiles 2 and 4) were found to be positively correlated with SUA and hyperuricemia. Higher levels of mercury and lead was associated with gout,
Zhang et al., 2021 [18]	Cohort	China	408 100% males	42.5 (33–53)	Gout	ND	Cadmium and lead	C and Pb were higher in gout than H.C. Cd levels were significantly associated with gout flare.

Appendix 2 (cont). Summary of the studies that evaluated toxic metals in several rheumatic diseases

Author, reference	Study design	Country	n/gender	Age (years)	Disease	Disease duration	Metal intoxication	Clinical features
Krishnan et al., 2012 [19]	Population-based cross-sectional	United States	290 gout from 6,153 individuals	64.7	Gout	ND	Lead	Gout was 6.05% (95% CI, 4.49% to 7.62%) among patients with the highest lead levels. Each doubling of lead levels was associated with an odds ratio of 1.74 (CI, 1.47 to 2.05) for gout and 1.25 (CI, 1.12 to 1.40) for hyperuricemia.
Halla et al., 1982 [20]	Cross-sectional	United States	42	ND.	Gout	ND	Lead	In 62% of patients, gout and plumbism were diagnosed simultaneously; in 26%, the plumbism preceded the gout; and in 12%, gout preceded the plumbis. EDTA was used with a good response.
Forte et al., 2018 [21]	Cross-sectional	Italy	27 vs. 30 HC 66.7% females	55.7± 14.3	SSc	8.11± 8.01	Al, Cd, Hg, and Pb in blood and urine	Al was lower in blood and increased in urine. Pb was increased in the blood. Hg in urine was associated with a higher severity of the disease.
Marie et al., 2017 [22]	Case-control	France	100 vs. 300 HC 78% females	52	SSc	2 years	Antimony, cadmium Lead, mercury, molybdenum, palladium, and zinc	The median values of the following metals were greater in SSc patients: antimony, cadmium, lead, mercury, and palladium.
Arnett et al., 2000 [23]	Cross-sectional	Canada	13 (anti-fibrillarin 11 SSc), 39 SSc, and 32 controls 92% females	46	SSc, Anti-fibrillarin	6 years	Urinary mercury	Mean urinary mercury was higher in positive anti-fibrillarin patients. Although, no difference was seen when patients with low creatine were excluded.
Motts et al., 2014 [24]	Cross-sectional	Brazil	371 30.7% females	ND.	Miners	ND	Mercury	Exposure to mercury and increased blood levels of 3760 autoantibodies. The following are the most significant proteins: interferon-induced transmembrane protein, signal peptide peptidase like 2B, triggered by retinoic acid 13, tumor necrosis factor ligand superfamily member 13, and antibodies to GSTA1.

Appendix 2. Summary of the studies that evaluated toxic metals in several rheumatic diseases

Author, reference	Study design	Country	n/gender	Age (years)	Disease	Disease duration	Metal intoxication	Clinical features
Gardner et al., 2010 [25]	Cross-sectional	Brazil	246 30% females	ND.	Miners	ND	Mercury	As compared to diamond and emerald miners who had no occupational exposure to mercury, mercury-exposed gold miners exhibited greater frequencies of detectable ANA and ANoA, higher titers of ANA and ANoA, and higher levels of IL-1 β, TNF α, and IFN.-y.
Stejskal et al., 2013 [26]	Transversal and prospective	Norway	15 Females	47.6 (34–66)	Fibromyalgia	11 (2–29) years	Nickel, inorganic mercury, cadmium and lead	All FM patients had positive test results for at least one of the metals examined. Nickel-related reactions were most common, followed by inorganic mercury, cadmium, and lead. Dental metal restorations should be replaced, and known sources of metal exposure should be avoided. After five years, 30% of patients still had FM, 20% had improved, and 50% no longer met the criteria for the F.M. diagnosis. All patients reported an improvement in their subjective health. This was connected with the in vitro normalization of reactions to metals.
Cemek et al., 2010 [27]	Cross-sectional	Turkiye	33 48.5% females	11.4± 3.82	Acute rheumatic fever	ND.	aluminum (Al) and barium (Ba) were lower, whereas the copper (Cu), beryllium (Be), cadmium (Cd), chromium (Cr), gallium (Ga), and strontium	Metals were similar to controls. Metals did not change after R.F. treatment.
Wronski et al., 1977 [28]	Case report	Germany	1 Female	50	PAN	33	Mercury	A dentist assistant chronically exposed to mercury had erethism, tremors, and mercurial psellism. Peripheral arterial circulatory disorders occurred in the course of the disease, as well as abdominal colic and polyneuropathy

Appendix 2. Summary of the studies that evaluated toxic metals in several rheumatic diseases

Author, reference	Study design	Country	n/gender	Age (years)	Disease	Disease duration	Metal intoxication	Clinical features
Fang et al., 2023 [29]	Cross-sectional	United States	1,375 OA and 468 RA from 9,735 51.1% females	50	OA RA	ND	Cd, Pb, and mercury	Cadmium (Cd) and lead (Pb) statistically grew the risk of total arthritis, O.A., and R.A.
Stejskal et al., 2015 [30]	Cross-sectional	Norway	38 92% females	51 (27–77)	SLE (n=0), R.A. (n=16), and S.S. (n=13).	ND.	The test menu for late hypersensitivity included inorganic and organic mercury, tin, copper, silver, gold, níquel, Pd, cadmium, lead, and titanium.	87% had a positive lymphocyte reaction to at least 1 metal and 63% to ≥2 metals. Control 43% (1 metal) and 18% (≥2 metals). The most frequent allergens were nickel, mercury, gold, and palladium.
Albert et al., 2004 [31]	Questionnaire	United States	53 (W.G.), 50 (O.A.), and 53 Gout; 50.9% females	61.8	WG, OA, and Gout	ND		Lead exposure was positively associated with W.G. as compared to OA and gout.
Yildiz et al., 2020 [32]	Case series	Turkiye	5 pediatric patients; 60% females	4, 6, 7, 9, 14	Pt. 1 and 2: PAN-like Pt. 3: asymptomatic Pt. 4 and 5: Erythromelalgia	2 (n=1) and 3 (n=2) weeks; 5 months (n=2)	Mercury	After 3 weeks of DMSA treatment, all symptoms improved. In addition, antihypertensive drugs were gradually reduced.
Guan et al., 2023 [33]	Cross-sectional	United States	514 arthritis from 2,174 individuals. 53.5% females	59.26± 13.2	Arthritis	ND	Cadmium (Cd), lead (Pb), mercury (Hg)	Increased risk of arthritis: Pb [OR (95% CI): 2.96 (2.18, 4.03), the p-value for trend (P-t) <0.001], Cd [OR (95% CI): 2.28 (1.68, 3.11), P-t <0.001]. Subgroup analysis showed that Pb and Cd ions significantly correlated with osteoarthritis and rheumatoid arthritis.
Stamp et al. 2015 [34]	Case-control	New Zealand	49 cases vs. 196 controls 53% males	64.9± 12.4	Granulomatosis with polyangiitis	11.3 years	Occupation exposure: brick/foundry worker, sand blaster, dental technician, mine/quarry worker	No association with metal exposure in the year prior.

ANA: Antinuclear antibodies; ANoA: Anti-nucleolar antibodies; SUA: Serum uric acid; Cd: Cadmium; Cu: Copper; HC: Healthy controls; Mn: Manganese; RA: Rheumatoid arthritis; SSc: Systemic sclerosis; OA: Osteoarthritis; PAN: Polyarteritis nodosa; Pb: Lead; WG: Wegener's granulomatosis; DMSA: Meso-2,3-dimercaptosuccinic acid; Zn: Zinc; ND: Not described.