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Mini-Review

Antimony: a cryptic metabolism disruptor ubiquitous in food contact materials

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Abstract

Antimony (Sb) is a group 15 metalloid that is used as a catalyst in the production of polyethylene terephthalate (PET) plastic, a common food contact material (FCM). PET accounts for over 44% of single-use beverage packaging units and is also used in the production of food trays, storage containers, and other items. Due to its frequent co-occurrence with other metals, Sb is also a common contaminant in crystalware, ceramics, and metal FCMs. In light of the increasing use of Sb-containing FCMs in modern society, a thorough evaluation of Sb's potential effect on public health is warranted. Burgeoning evidence suggests Sb is linked to common cardiometabolic conditions, including dyslipidemia, obesity, diabetes, hypertension, heart failure, and atherosclerotic cardiovascular disease. Thus, this review aims to (1) perform a comprehensive systematic assessment of Sb migration from FCMs into foodstuffs and food simulants, (2) obtain an overview of antimony-related health risks, and (3) inform the generation of harm-reduction guidelines at the individual and systems levels.

Key Words antimony, food contact material, plastics, cardiometabolic, polyethylene terephthalate, migration

Antimony (Sb) is a group 15 metalloid used as a catalyst for producing polyethylene terephthalate (PET). Low concentrations of Sb are dispersed into the plastic matrix to produce rigid food packaging [1]. Over 70 million tons of PET are produced globally per year, with production increasing by ~4% annually [2, 3]. Numerous studies show that Sb can migrate into packaged foods and beverages over time [4-6]. Indeed, Sb has been shown to be one of the most concentrated metal leachates released from plastic food containers at high temperatures [7]. Thus, PET packaging is likely an important source of oral Sb exposure. Given the widespread use of PET plastics in food and beverage packaging, Sb exposure is a potentially significant public health concern [8].

The growing prevalence of Sb in plastic products means that human exposure to Sb is at unprecedented levels [9]. Sb is a heavy metalloid that is toxic at even low concentrations [10, 11]. Epidemiological and experimental evidence has linked Sb exposure to several adverse health effects, particularly cardiometabolic disorders such as diabetes [12-17], obesity [18, 19], hypertension [20-27], and atherosclerotic cardiovascular disease (ASCVD) [28-31].

More than half a billion people suffer from cardiometabolic conditions [32], with annual economic costs projected to exceed $1 trillion by 2030 [33, 34]. While genetic predisposition, excess energy intake, and insufficient energy expenditure contribute to the rising prevalence of cardiometabolic disorders, these factors fail to fully account for the rising tide of disease. Over the last two decades, environmental toxicants have emerged as factors promoting disease susceptibility [35, 36]. Indeed, over 1000 chemicals have been identified as endocrine-disrupting chemicals (EDCs) [37], with many linked to cardiometabolic dysfunction [38-40]. EDCs are defined by the Endocrine Society as "an exogenous chemical, or mixture of chemicals, that can interfere with any

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aspect of hormone action" [41]. Burgeoning data now clearly implicate EDCs in cardiometabolic dysfunction through various disruptions in metabolic homeostasis [42]. Consequently, exposed individuals are likely at higher risk of developing cardiometabolic disorders, while disproportionate exposures among vulnerable populations may contribute to health disparities [43-45]. Thus, identifying and reducing exposures to EDCs may reduce overall disease burden and improve health equity. The analysis presented herein focuses on Sb, an underappreciated EDC found in food contact materials (FCMs) and food contact articles (FCAs).

With Sb-containing FCMs becoming ubiquitous in the processing, packaging, storing, and consumption of food and beverage products, a thorough investigation of Sb-associated health risks is warranted. The World Health Organization (WHO) recommends <20 μg Sb/L drinking water and has established a tolerable daily intake of 6 μg Sb/kg body weight [46]; however, region-specific guidelines differ. For example, the European Union (EU) had set their Sb drinking water limit at 5 μg/L, but recently raised this to 10 μg/L [47], whereas the US Environmental Protection Agency (US EPA) recommends <6 μg/L drinking water and <0.35 μg Sb/kg body weight per day for oral exposure [48]. Although US EPA does not currently have a regulatory limit for Sb migration into food, most studies show migration levels below the limits set by WHO (20 ppb; 0.02 mg/kg) and the EU (40 ppb; 0.04 mg/kg). Even so, a majority of studies reporting minimal Sb leaching (<2.5 μg/L) from beverage bottles only tested water under typical storage conditions [49-52]. Leaching is substantially enhanced with increasing acidity, temperature, and storage time, resulting in levels greater than 5 μg/L [4, 52-54]. Despite this marked variability in Sb migration, cumulative contact with Sb-containing FCAs has yet to be evaluated; moreover, the cardiometabolic effects of Sb were not assessed prior to its authorization for use in FCMs. Hence, in order to facilitate determination of Sb's risk to current consumers, the Database on Migrating and Extractable Food Contact Chemicals (FCCmigex) [55] was used to (1) perform a comprehensive assessment of Sb migration from FCMs into foodstuffs and food simulants, (2) obtain an overview of antimony-related health risks, and (3) inform the generation of harm-reduction guidelines at the individual and systems levels.

Methods

Antimony-containing food contact articles: literature search

Scientific reports analyzing Sb migration from FCAs were retrieved from FCCmigex, version 3 [55]. The database was filtered for references that analyzed the migration of Sb from all types of FCAs where Sb was detected in food and/or food simulants (Fig. 1). Migration is generally considered a proxy for human exposure, as chemicals migrating from FCMs are very likely to be ingested with foodstuffs. In total, 54 references matched filter criteria for Sb migration into food or food simulants. Abstracts were filtered to remove duplicates, non-English publications, and extraction experiments. For all 40 retained references, we mapped experimental details and migration results (eg, duration, temperature, type of food/food simulant, type of FCM, and Sb migration levels).

Data extraction and compilation of Sb levels

We compiled the following information from the selected studies on Sb migration from FCMs:

- Bibliographic information;
- Chemical form of Sb detected, eg, elemental form (Sb) or antimony oxide form (Sb_2O_3);
- Migration limits as specified by EU and US legislation, ie, specific migration limit set by Commission Regulation (EU) No. 10/2011 along with the reference number of the substance as given in the Union list (FCM No.) and allowable levels for bottled water in the US [56] since no migration limits are listed for "substances added to food";
- Initial concentration of Sb in FCAs before migrating (if available);
- Detected Sb concentration in food/food simulant, including the limit of detection (LOD) expressed in mg/kg;
- Number of analyzed samples for the given migrated concentration—clarifying whether this number referred to replicates from the same sample or to distinct samples;
- Migration conditions and factors that were investigated during migration experiments, eg, storage duration (usually days), storage temperature, ultraviolet radiation exposure, pH, or any other condition applied during migration testing;
- Food simulant or food sample into which Sb was found to migrate;
- Chemical analysis method used to determine migration levels;
- Type of packaging material, eg, PET, metal, glass, crystalware, etc.;
- The source of the food packaging material, ie, whether it was virgin or recycled, including the recycled content (if available);
- The use of PET article, ie, whether it was single-use or repeat-use;
- Reported form of food packaging article, eg, bottle, preform, pellet, container, tray, films, etc., including characteristics such as capacity/color (if available);
- Purchase location of FCA (if available); and
- The lifecycle stage depending on the migration conditions and the source of food packaging material, eg, migration experiments under specified storage conditions refer to the stage of storage and distribution, while migration experiments in virgin food packaging articles that do not consider any storage conditions refer to the stage of production, and migration experiments in recycled food packaging articles refer to the stage of reprocessing.

Urinary antimony levels in the USA

We assessed the average concentration of urinary Sb in a large nationally representative sample of the US population [57]. Briefly, the National Health and Nutrition Examination Survey (NHANES) is a cross-sectional survey representing the general US population that has been conducted continuously in two-year cycles beginning in 1999. Demographic, dietary, physical examination, laboratory, and questionnaire data are collected from

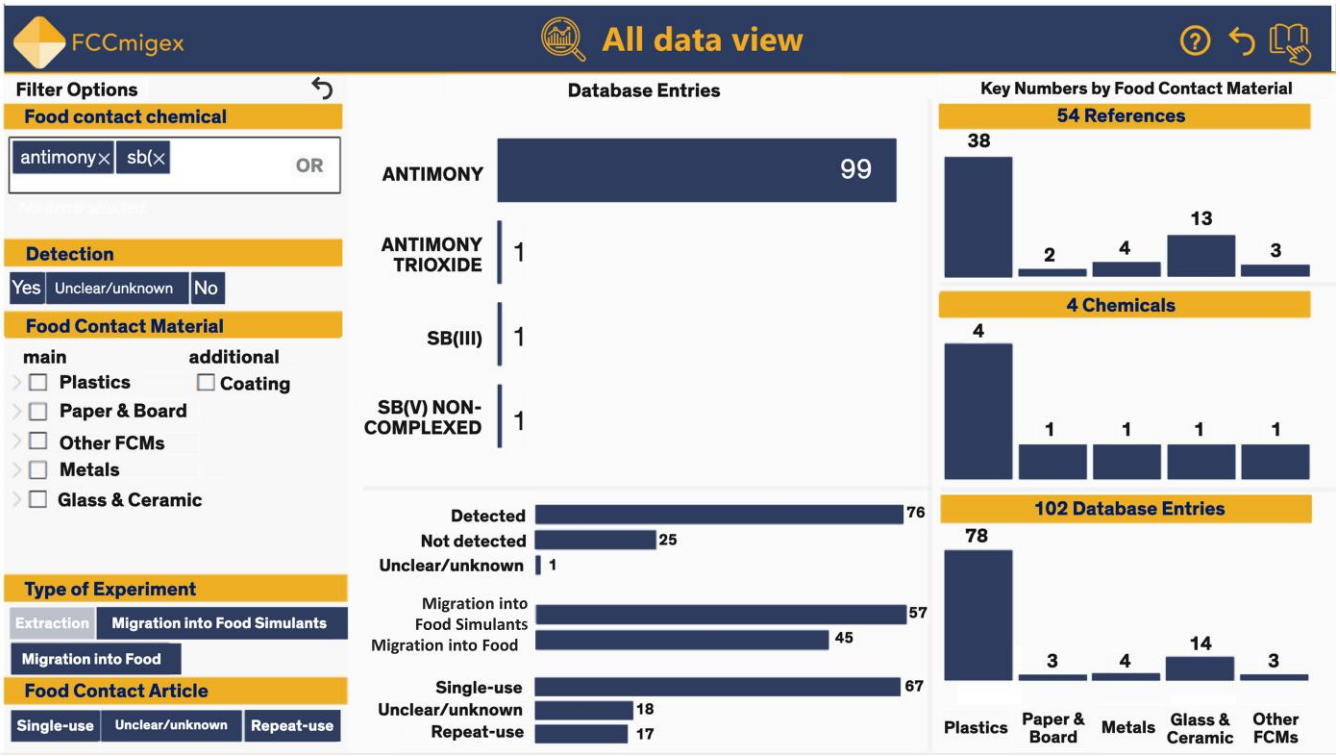

Figure 1 Sb and food packaging: FCCmigex database results. Representative image of the FCCmigex database following filtration for references that analyzed the migration of Sb from all types of FCAs (single-use, unclear/unknown, or repeat-use). This included 102 database entries (78 plastics, 3 paper & board, 14 glass & ceramic, and 3 other FCMs) from 54 references matching filter criteria. The total number of references was reduced to 40 following abstract review for duplicates, non-English articles, and extraction experiments. Figure redrawn in BioRender. Wang, L. (2026) https://BioRender.com/32yo4rf.

each participant with complex sampling and survey weighting. Utilizing four NHANES cycles from 2011 to 2018, 11 457 participants eligible for urinary metal measurements were assessed for Sb levels. The eligible sample included all examined participants aged 3 to 5 years and a random one-third subsample of participants aged 6 years and older. Accounting for survey design and outliers, we summarized geometric mean and 95% confidence interval for urinary Sb among 10 901 NHANES participants without missing urine measurements. The lower LOD for Sb in urine utilizing mass spectrometry was 0.022 μg/L. Among participants without missing samples, 23.92% of samples were below the LOD and were assigned a concentration of the LOD divided by $\sqrt{2}$. Averages were estimated using SAS software version 9.4 (SAS Institute Inc., Cary, NC).

Antimony-related health risks: literature search

Thirteen Medical Subject Heading (MeSH) terms were chosen and combined as described in Fig. 2. This returned 694 PubMed results from 1954 to May 12, 2025. Of these, 34 were non-English articles and 4 were duplicates; these 38 articles were excluded from analysis. The remaining 656 articles underwent title review to determine relevance to cardiometabolic disease. This led to the exclusion of 444 additional articles that were focused on topics outside the scope of this review. The remaining 212 articles were assessed based on abstract content. Of these articles, 127 were excluded for (1) not being focused on Sb, (2) not being focused on cardiometabolic disease and associated comorbidities, and/or (3) being editorials or review articles. This generated a total of 85 articles for analysis. Of these, 3 were *in vivo* studies, 4 were case studies/case reports, 11 were case-control studies, 28 were cross-sectional studies, and 39 were cohort studies.

Results

Human biomonitoring for Sb

Utilizing NHANES data from 2011 to 2018, the geometric mean for urine Sb was 0.0473 μg/L (95% CI: 0.0462, 0.0483, LOD: 0.022 μg/L) among 10 901 participants weighted to represent the general U.S. population. This is similar to data reported by the 2009-2011 Canadian Health Measures Survey, for which the geometric mean urinary Sb concentration was 0.048 μg/L (95% CI: 0.046, 0.050) for an analytical sample of 6311 individuals between the ages of 3 and 79 years; in this analysis, 20% of values were below the LOD of 0.02 μg/L [58]. Findings from the 2017-2018 China National Human Biomonitoring Survey (CNHBS) were also comparable: 0.05 μg/L (95% CI: 0.02,0.09) for a population of 11 037 individuals; however, the LOD was higher in this study (0.045 μg/L for urine), with 48.9% of subjects having urinary Sb levels below the LOD [21]. In contrast, blood measurements for the CNHBS population revealed an average Sb concentration of 2.35 μg/L (LOD of 0.03 μg/L). These data are summarized in Table 1. Population-based biomonitoring data could not be found for Japan, but a recent analysis of global

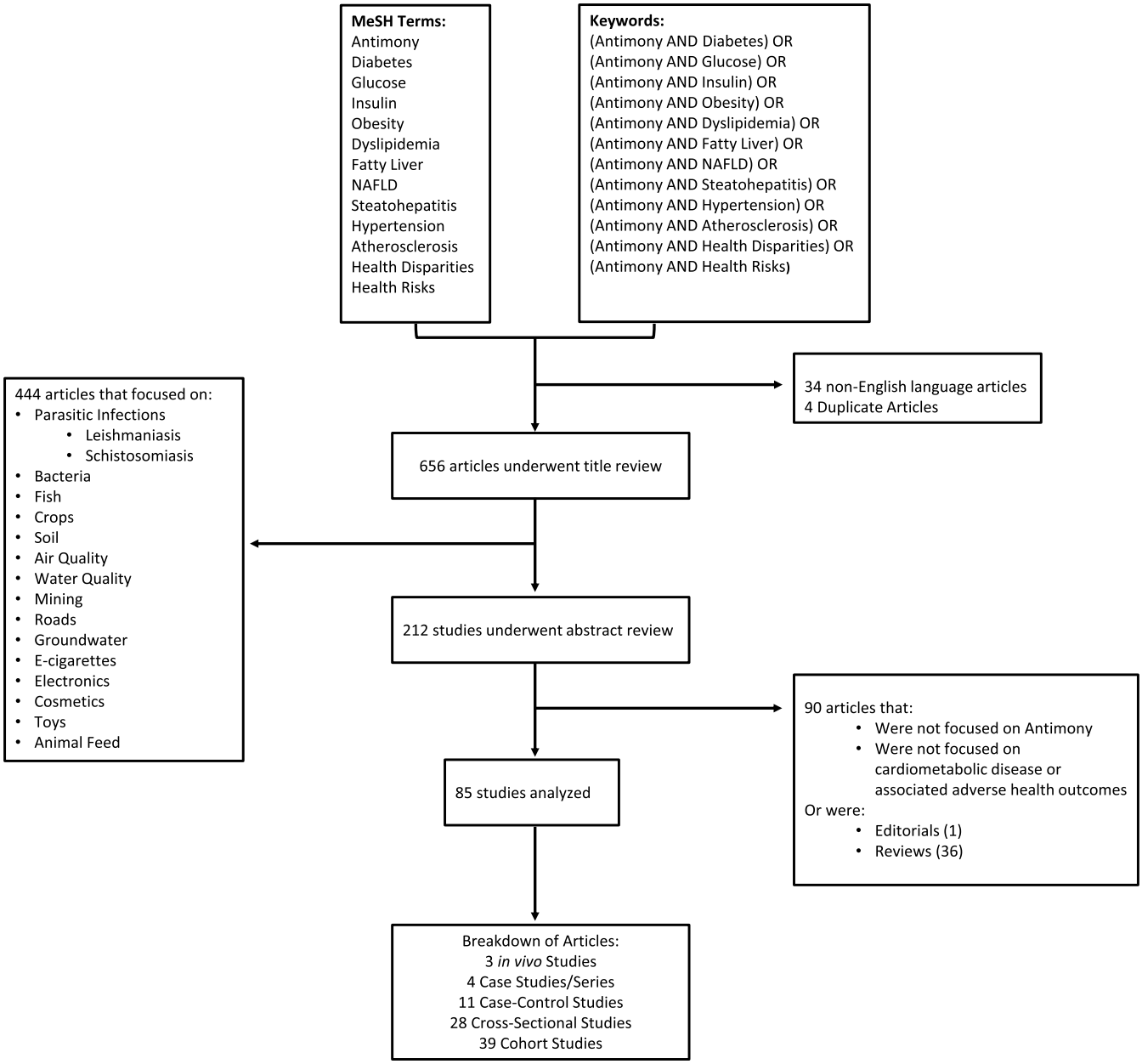

Figure 2 Sb and cardiometabolic disease: Flowchart of systematic literature review in PubMed. Representative chart of MeSH Terms, keywords, and filtering mechanisms utilized to review current literature linking Sb and cardiometabolic health outcomes. The initial search yielded 656 articles, with 444 articles being removed from further review due to their focus on environmental outcomes, toys, cosmetics, or parasitic infections. Of the remaining 212 studies, 53 articles did not directly examine antimony or cardiometabolic disease outcomes, and 37 references were not primary literature. The final 85 articles meeting the inclusion criteria included: 3 in vivo studies, 4 case studies/series, 11 case-control studies, 28 cross-sectional studies, and 39 cohort studies.

DNA methylation in umbilical cord blood showed a consistent positive association with Sb levels [59].

Antimony exposure via food contact articles

All literature cited in this section was collected from the FCCmigex database search for Sb. Sb migration levels vary with changes in temperature, type and acidity of foodstuff, and time [6, 50, 53, 54, 60-77]. Sb leaching from PET also depends on the nature of the Sb migrant (ie, its chemical speciation) and the morphology of the plastic polymer [5]. Migration also increases with greater use of Sb-containing recycled plastic waste in FCAs [78, 79]. Higher baseline Sb levels in FCAs raises concern for increased Sb leaching during the storage of acidic foodstuffs like soft drinks and juices [61, 74, 77] as well as during heating of foodstuffs in Sb-containing plastic containers [75]. Although the potential health risks of Sb exposure from PET bottles have been considered acceptable in most cases [49-51], some samples exceeded established Sb limits even under normal storage conditions [61, 67-69]. Therefore, it is possible that total exposures from PET and other FCMs are higher than the guideline values.

Table 1 Human biomonitoring for Sb in urine and blood by country

Country	Limit of detection for Sb (μg/L)	Urinary Sb concentrations (μg/L)	Blood Sb concentrations (μg/L)
USA (NHANES)	0.022	0.0473 (95% CI: 0.0462, 0.0483)	Not available
Canada (CHMS)	0.02	0.048 (95% CI: 0.046, 0.050)	Not available
China (CNHBS)	Urine: 0.045 Blood: 0.03	0.05 (95% CI: 0.02, 0.09)	2.35 (95% CI: 1.92, 2.93)

Compilation of urine and blood biomonitoring for Sb from publicly available data and published literature for the USA, Canada, and China.

Critically, few studies have been performed to assess cumulative Sb exposure from PET and other FCMs. This is of special concern due to the rise in plastic usage and the lack of data for baseline exposure estimates [80, 81].

FCCmigex can be used to fill such data gaps. According to the FCCmigex database (version 3, including data published by May 2025), Sb migration into foods and/or food simulants has been detected from plastics, glass, ceramics, metal, and other/undefined FCMs. A search for "Antimony" and "Sb" on May 12, 2025, returned 54 results. Of the 40 relevant migration papers, 33 examined PET plastics used to generate beverage bottles and ready-made meal trays. In 1995, an early study on Sb migration from plastic FCMs reported Sb levels of 1.1 to 3.9 μg/kg food simulant in migrates from PET samples; however, in migrates of non-PET polymers, the Sb levels were below the LOD [82]. Since then, dozens of migration studies have analyzed Sb migration from PET, but also from glass, ceramics, paper, and metal [75, 83-86]. Following data extraction from the compiled literature, we found that approximately 66% of experiments tested migration into pure or distilled water, while a minority of experiments tested acidified water/beverages (23%) or other consumed food products (11%). Ranges of migration levels are summarized in Table 2 for different FCMs under various experimental conditions. Migration appears to vary by FCM type, as migrates from PET showed higher Sb levels than glass bottles [63, 86]. Regardless of the material, Sb levels below 20 μg/kg food or food simulant were detected in most of the experiments [60, 64, 87, 88]. However, we identified multiple studies in which Sb levels >100 μg/kg food simulant were reached in migrates of inorganic FCMs, such as crystal glass [89] and glazed ceramics [90]. Sb was released from stainless steel sheets into acidic food simulants at varying levels depending on the material's grade, reaching concentrations between <0.1 and 4 μg/kg food simulant [85]. Sb migration levels up to 241, 88, and 38 μg/kg food were observed in doughs prepared in PET baking dishes, meat and fish roasted in PET bags, and ready-to-eat meals heated in PET trays, respectively [5]. A separate study from the same group reported an increase of 1.7 to 14.9 μg Sb per kg food in heated ready-made meals [6]. Collectively, these data indicate that despite high variability in migration due to differences in study conditions, FCMs are a potentially significant source of Sb exposure.

Antimony and cardiometabolic disease

Given the increasing use of Sb in FCMs, we proceeded to synthesize the available data on Sb exposure and cardiometabolic outcomes. Epidemiological studies have linked Sb exposure to various health conditions, including impaired fasting glucose, insulin resistance, obesity, hypertension, and dyslipidemia [91]. Although it is difficult to examine the isolated health effects of Sb due to its frequent co-occurrence with other nonessential ("toxic") metals in mixtures [92], emerging human and animal data indicate a role for Sb in the development of multiple cardiometabolic disorders. A summary of these findings is illustrated in Fig. 3.

Diabetes

While five studies showed no significant link [93-95] or even negative associations [96, 97] between Sb and diabetes, a number of other studies indicated that Sb may be diabetogenic. In gestational diabetes mellitus and type 2 diabetes mellitus, elevations in blood glucose stem from insufficient insulin secretion from β-cells, a process that may be induced or amplified by peripheral insulin resistance. Impairments in glucose homeostasis manifest as elevated fasting and postprandial blood glucose levels with accompanying increases in hemoglobin A1c (HbA_{1C}) levels, an integrative marker of glycemic status. Sb exposure has been associated with elevated HbA_{1C} in adolescents, particularly males [98]. A cross-sectional study in Wuhan, China, also linked Sb exposure to increased diabetes risk, particularly in the highest quartile of exposure [12]. However, the association was lost after adjustment for anti-hyperglycemic medication use and history of diabetes, suggesting that Sb-mediated effects may be influenced by diabetes status [12], highlighting the need for longitudinal studies stratified by glycemic status. Data from a 1999-2010 NHANES analysis showed positive associations between Sb levels and insulin resistance as assessed by the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) [13]. Similarly, a 2020 analysis of blood from subjects with polycystic ovary syndrome revealed positive correlations between Sb levels and both fasting plasma glucose and HOMA-IR [99]. Positive associations between Sb and fasting plasma glucose were similarly noted in a cohort of women from the Manganese-Exposed Workers Healthy Cohort in China [17]. Several studies in pregnant women also noted positive associations between Sb and gestational diabetes risk [15, 93, 94, 97]. Supporting this epidemiological data, rodent models suggest that Sb can increase serum glucose levels in female rats at high levels of exposure (60 mg Sb/kg/day for 28 days) [100], though an earlier study indicated that 90 days of exposure to Sb at approximately 0.64, 6.13, and 45.69 mg/kg/day can lower glucose levels in female rats [101]. Importantly, neither rodent study examined dynamic changes to glucose homeostasis or alterations in insulin levels, critical areas for future investigation. Collectively, these data indicate that Sb may have the capacity to disrupt glucose homeostasis, including during sensitive windows of development.

Table 2 Summary of Sb migration levels for different FCMs under various experimental conditions

Material	Below LOD, %	Range of Sb migration levels (μg Sb/kg food or food simulant)
Paper	0%; (0/9)	1×10^{-3} to 3×10^{-2}
Plastic	7%; (56/802)	1.1×10^{-7} to 241
Glassware	66.7%; (6/9)	4×10^{-5} to 2.8×10^{-2}
Crystalware	8.7%; (4/46)	1.6×10^{-1} to 170
Ceramics, Porcelain, Earthenware	29.7%; (11/37)	3.6×10^{-3} to 141
Metals	0%; (0/8)	1×10^{-1} to 4

The FCCmigex identified Sb in several FCMs. The number of experiments that reported migration levels below the LOD are expressed as a percentage relative to all experiments examining migration levels in each FCM. Minimum and maximum reported migration levels (μg/kg) are listed for each FCM.

Obesity

The relationship between Sb and obesity remains inconclusive. An early analysis of 1999-2002 NHANES data showed no significant relationship between Sb and waist circumference or body mass index [102]. A 1999-2011 NHANES study also found no significant correlation between urinary Sb and obesity in children aged 6 to 19 years [103]. Additionally, data from the Guangdong Provincial Residences' Chronic Disease and Nutrition Surveillance Survey showed no significant association between Sb exposure and obesity measures [104]. Despite these null findings, a 2003-2014 NHANES study found positive associations between Sb-containing metal mixtures and obesity, hypertension, and type 2 diabetes mellitus; however, that study did not identify Sb exposure alone as a risk factor [19]. A more recent analysis using NHANES 1999-2016 data revealed a curvilinear relationship between urinary Sb levels and obesity, with moderate Sb levels associated with obesity [18]. In a study of childhood cardiometabolic risk, Bayesian Kernel Machine Regression modeling revealed a negative association between Sb and levels of leptin, a hormone critical for promoting satiety; this finding may indicate a mechanism by which Sb can alter body weight regulation [105]. Given the current state of the evidence, longitudinal studies are needed to fully elucidate the impact of Sb exposure on adiposity.

Liver disease

Hepatotoxicity is a well-documented side effect of pentavalent antimonial drugs used to treat leishmaniasis, the use of which result in high Sb exposure (~20 mg Sb/kg/day for 20 to 30 days) [106]. However, hepatic dysfunction has also been observed at lower exposure levels. Epidemiological analyses linked elevated plasma Sb levels (>0.09 μg/L) to increases in total and direct bilirubin in an adult Chinese population [107]. Bilirubin is a by-product of red blood cell (RBC) breakdown that is enzymatically conjugated by hepatocytes and excreted into the bile. Thus, elevations in bilirubin may indicate impairments in hepatic bilirubin metabolism and/or biliary excretion. Complementary to findings of Sb associations with bilirubin levels, a recent NHANES study (2003-2018) demonstrated that urinary Sb (0.03-0.09 μg/L) was positively linked to metabolic dysfunction-associated steatotic liver disease (previously "nonalcoholic fatty liver disease") [108]. In animal models, a study in rats examining a range of Sb exposures [0, 0.06, 0.6, 6, and 60 mg Sb^{3+}/kg/day for 28 days] demonstrated an increase in liver-to-body weight ratio at the highest dose in both sexes, with an increase in relative liver weight also seen in female rats exposed to 6 mg Sb/kg/day [100]. In this same study, liver enzymes were also altered. Alkaline phosphatase (ALP) levels were reduced in male rats at all doses except the 6 mg Sb/kg/day dose, while the aspartate aminotransferase (AST)-to-alanine aminotransferase (ALT) ratio (AST:ALT) was reduced at all doses in female rats. These alterations in liver enzymes suggest a capacity for Sb to induce liver dysfunction, as ALP is an enzyme crucial to nutrient processing in the liver and altered AST:ALT ratios can be indicative of liver damage. This supposition is reinforced by blood metabolomics analyses from these rats indicating dose-dependent disruptions in glucose and lipid metabolism [100]. Evidence of Sb-induced alterations in liver health are further supported by a study of Kunming mice exposed to 15 mg Sb/kg/day for 60 days. Sb-exposed mice exhibited increased liver-to-body weight ratio, elevations in serum ALT, AST, and ALP, and irregular nuclei and chromosome marginalization in hepatocytes [109].

Hypertension

Hypertension is a state of chronic blood pressure elevations that is a potent driver of cardiovascular disease. Studies of the 2009-2010 and 2011-2012 NHANES cycles showed a significant association between Sb exposure and higher blood pressure [23, 24]. Evidence from a cohort of children in China showed similar findings, with higher Sb levels positively correlated with systolic blood pressure (SBP), mean arterial pressure (MAP), and odds of having hypertension; moreover, there were significant synergistic interactions between Sb and arsenic (As), another Group 15 metalloid linked to multiple cardiometabolic disorders [22]. In the Alberta Pregnancy Outcomes and Nutrition Cohort, there was a trend toward a positive association between Sb levels and pregnancy-associated hypertension ($P < .10$) [110]. A case-control study in postpartum women in Tehran also revealed that increases in umbilical cord blood Sb levels were associated with a markedly increased risk of preeclampsia [111].

In contrast to this work, data from five other studies showed no significant associations between blood pressure and Sb exposure [20, 21, 112-114]. This heterogeneity across studies could be due to various factors, including lifestyle, potential nonmonotonic dose–response relationships, or complex interactions of toxic metal mixtures. For example, high SBP correlated with low Sb levels, but high cadmium (Cd) and lead (Pb) levels, suggesting a toxicological interaction between the three metals in one study [25]. Experimental studies that test various metal mixtures and Sb exposures are needed to conclusively delineate a role for Sb exposure in the development and/or severity of hypertension.

Atherosclerotic cardiovascular disease

ASCVD is caused by the accumulation and modification of lipoproteins that results in the migration and activation of immune and smooth muscle cells in the subendothelial space of arterial walls;

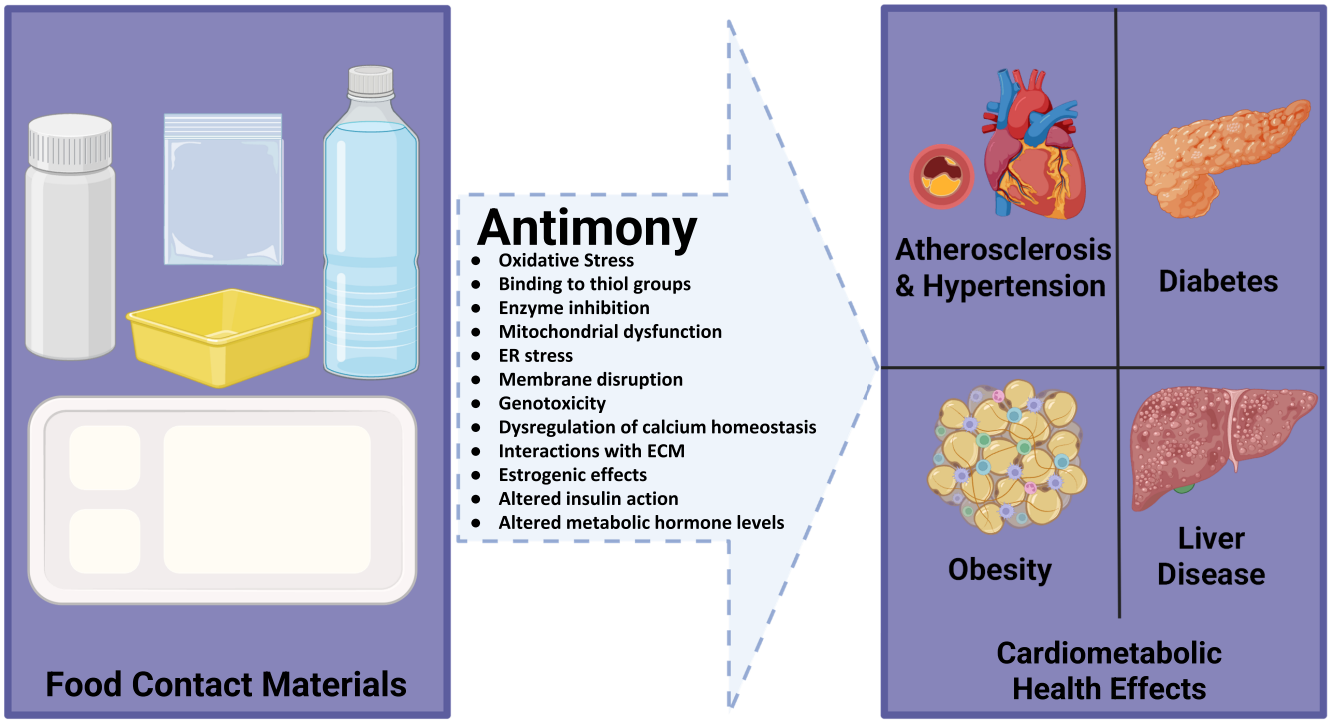

Figure 3 Sb and associated cardiometabolic health risks. Sb is a common catalyst in the manufacturing of PET plastic FCMs, and the current literature links Sb exposure to a variety of adverse health effects, including atherosclerotic cardiovascular disease, hypertension, diabetes, liver disease, and obesity. Potential mechanisms of Sb-mediated toxicity are listed within the dashed arrow. ER, endoplasmic reticulum; ECM, extracellular matrix, ROS, reactive oxygen species. Created in BioRender. Wang, L. (2025) https://BioRender.com/yjlawz8.

these atherosclerotic plaques can be flow-limiting and are susceptible to acute rupture and clot formation, resulting in major adverse cardiovascular events. Sb has been identified as an atherosclerotic risk factor in several studies. Analyses from Spain's Hortega Study and NHANES (1999-2006) support an association between Sb exposure and cardiovascular disease incidence [27, 30, 115]. In addition, scalp hair concentrations of Sb correlated with atherosclerotic plaque severity in the left main coronary artery in a Polish cohort [116]. Results from a Wuhan-Zhuhai cohort in China support these findings, with urinary Sb positively associated with increased 10-year ASCVD risk [28]. Indeed, several studies have positively correlated Sb exposure with increased risk of cardiovascular disease mortality [117-119]. This is further supported by evidence from the Aragon Workers Health Study, which identified Sb as a potential epigenetic modifier and atherosclerotic risk factor in car assembly plant workers [120, 121]. In metal mixture analyses using NHANES data (2003-2016), Sb was shown to be one of the strongest contributors to CVD risk [26]. In the Wuhan-Zhuhai Adult Cohort, Sb was also positively associated with mean platelet volume, which may be an early biomarker for cardiovascular damage [122]. Thus, there is mounting evidence linking Sb exposure to ASCVD risk.

Molecular mechanisms underlying the health effects of Sb

The mechanisms by which Sb acts are incompletely elucidated; however, there appear to be many parallels with arsenic (As). For example, transcriptional and proteomic profiles of human epidermal keratinocytes exposed to As^{3+} or Sb^{3+} show significant overlap in differentially expressed genes, suggesting similar mechanisms of toxicity [123]. Much like As, Sb toxicity is dependent on its speciation and oxidation state, with trivalent Sb^{3+} compounds showing greater toxicity than pentavalent Sb^{5+} compounds. The pentavalent state predominates under oxidizing to slightly reducing conditions, while the trivalent form predominates under anaerobic conditions and is often the form released during anthropogenic activities. Intracellular reduction of Sb^{5+} compounds is possible [124], either occurring through an enzymatic pathway as observed in Leishmania parasites [125] or nonenzymatically via interaction with small thiols such as trypanothione or glutathione [126]. Sb exposure, especially Sb^{3+}, generates reactive oxygen species (ROS) that can overwhelm cellular antioxidant defenses and induce oxidative stress with associated macromolecular damage [127]. Direct interactions may also occur, as Sb can bind thiol (-SH) groups on proteins. Thus, Sb can have diverse effects on biological systems, including DNA damage; inhibition of enzyme activity; membrane disruption; and modulation of energy metabolism, including mitochondrial dysfunction [124, 128, 129]. Sb has been shown to be genotoxic in the bacterial reverse mutation test (Ames test) and in a chromosomal aberration test in cultured mammalian cells [130]. In yeast, Sb^{3+} inhibited DNA double-strand break repair and distorted cytoskeletal architecture [131]. Sb-induced oxidative DNA damage has been noted in zebrafish [132] and in occupationally exposed humans as well [133].

Redox imbalance resulting from oxidative stress [134-136], increased endoplasmic reticulum stress, and disruptions in

calcium homeostasis leading to apoptosis [137] have all been highlighted as molecular mechanisms underlying Sb-induced metabolic dysfunction and cardiotoxicity [138]. For example, exposure to Sb^{3+} led to an increase in cardiac calcium currents, which can cause QT prolongation and increase cardiac arrhythmia risk [139]. This effect could be due to Sb's high affinity for sulfhydryl groups [124], which can lead to oxidation of cysteine residues on proteins [129].

Accumulating evidence suggests that Sb also has estrogenic effects, likely occurring through interactions with the estrogen receptor that disrupt normal sex hormone signaling. In human breast cancer cells, the transcriptional profile generated by 1 μM antimony chloride showed a 60.9% match with 1 nM 17-β-estradiol [140]. The relative proliferation effect of antimony on breast cancer cells was also 49.2% that of 10 nM 17-β-estradiol [140]. More recently, it has been shown that Sb^{3+} causes reproductive defects in female zebrafish, including reductions in mature oocytes and a state akin to polycystic ovary syndrome with accompanying ovarian fibrosis [141]. Fish exposed to Sb exhibited elevated levels of gonadotropin-releasing hormone (GnRH), follicle stimulating hormone (FSH), and luteinizing hormone (LH) with a decrease in their estradiol (E2)-to-testosterone (T) (E2:T) ratio [141]. Mechanistically, Sb appeared to activate WNT/β-catenin and TGF-β/Smad pathways to promote extracellular matrix secretion [141]. Given that dysfunction in these pathways is commonly seen in cardiometabolic diseases [142, 143] and that several other estrogenic endocrine disruptors are linked to obesity and related metabolic complications [144], further interrogation of Sb-related cardiometabolic toxicity is warranted. Critically, the proposed molecular mechanisms underlying Sb toxicity are complex and diverse. Indeed, some effects may only occur at higher exposures (eg, with Sb-containing medications), while other negative impacts may be seen at lower levels of exposure relevant to the general population. Identifying Sb's mechanisms of toxicity across exposure groups will be essential for characterizing the broader threats of Sb exposure and for developing intervention strategies to mitigate those risks.

Environmental disparities and health inequities

Cardiometabolic disorders are a significant driver of morbidity and mortality, and disadvantaged populations are disproportionately affected [145]. An analysis of NHANES data (2005-2006) found a correlation between higher urinary Sb, bisphenol A, and pesticide levels with greater food insecurity in people with diabetes, respiratory, liver, or mental health disorders [146]. These findings may be related to the prevalence of food deserts in lower-income areas that result in greater consumption of packaged foods. Higher exposures may also be a consequence of the localization of industrial activity in low income communities and communities of color [147]. Analysis of pregnant women in the northeastern USA showed that higher nonessential metal exposures were associated with areas of higher crime, greater diversity, lower educational attainment, lower household income, and higher poverty; moreover, Black/Black-Hispanic women had Sb levels that were 35% higher than non-Hispanic White women, while Hispanic women had Sb levels that were 38.3% higher than their non-Hispanic White counterparts [148]. Such exposures in pregnant women pose particular concerns for gestational complications and long-term outcomes in the offspring of women exposed to high levels of Sb. Indeed, evidence from a lower-income Hispanic pregnancy cohort in Los Angeles showed that Sb is a strong predictor of birth weight for gestational age, with moderate to high concentrations associated with lower birth weight [149]. Based on the Developmental Origins of Health and Disease hypothesis that posits early life stressors can lead to long-term adverse health effects [150], these studies suggest that higher developmental exposure to Sb could contribute to a greater lifetime burden of disease in vulnerable communities. Further work is needed to clarify the full impact of Sb exposure disparities on cardiometabolic and other health inequities.

Perspectives and conclusions

Available migration data for Sb show several conditions under which WHO and EU regulatory limits are exceeded, particularly when the foodstuff is acidic or stored at high temperatures. Sb migration was highest in plastic FCMs, but migration levels were also notably high for ceramics, porcelain, earthenware, and crystalware. In contrast, glassware, paper, and metal showed the lowest migration levels. Collectively, these findings indicate that FCMs represent important yet modifiable sources of Sb exposure for the general population.

Although the epidemiological evidence is somewhat inconsistent, mounting data link Sb to adverse cardiometabolic health. Animal studies further demonstrate that Sb may induce cardiometabolic dysfunction, and mechanistic work strengthens concerns about Sb's molecular toxicity. While additional studies are needed to refine our understanding of exposure sources, clarify mechanisms of action, and establish appropriate regulatory limits, efforts to reduce exposure to known Sb sources is warranted to protect human health under the precautionary principle. While the exact contribution of FCMs to overall Sb exposure remains uncertain, current migration data support prioritizing use of glassware and metal containers over PET plastics. Although paper products show low migration rates, they remain understudied and carry competing exposure risks from organic EDCs like bisphenol A.

To our knowledge, there is currently no established No Observed Adverse Effects Level for human exposure to Sb; however, the Agency for Toxic Substances and Disease Registry Toxicological Profile (ATSDR) cites 0.06 mg Sb/kg/day in rats based on hypoglycemia endpoints [151]. More research is needed to define a No Observed Adverse Effects Level for humans. In the meantime, health professionals should advise reducing consumption of foods packaged in plastics and minimizing the use of plastic storage containers. Such recommendations may be difficult in resource-limited settings overburdened by other social and structural determinants of health, but it remains important to provide harm-reduction strategies whenever possible. Such strategies should include the entire healthcare team (eg, nutritionists, social workers) to help patients identify safer food sources and reduce toxicant exposure.

Further research is needed to clarify links between Sb and cardiometabolic outcomes in longitudinal cohorts. These studies

should carefully consider the matrix in which Sb is measured, as a Swedish study found high week-to-week variability in urine Sb, potentially as a consequence of Sb's long biological half-life and differential partitioning into various tissues [151, 152]. Indeed, blood Sb levels in the CNHBS population were substantially higher than urine levels, suggesting blood may be a more accurate measure of systemic Sb levels [21]. Overall, more comprehensive incorporation of different biological matrices (eg, blood, urine, hair, and toenails) as well as Sb speciation [Sb^{3+} vs Sb^{5+}] could greatly empower future investigations of this understudied metalloid.

While individual-level interventions matter, addressing environmental health threats requires systems-level solutions. To address Sb-associated health risks, such approaches should include improving PET plastic design, promoting design-for-recycling principles, replacing Sb as a catalyst with safer alternatives, and reducing Sb contamination in recycled plastics while minimizing health and safety tradeoffs and avoiding regrettable substitutions. Furthermore, biomonitoring initiatives should be strengthened with attention to the full spectrum of Sb-associated adverse health effects (cardiometabolic toxicity, endocrine disruption, cancer, etc.). Collectively, such comprehensive efforts could substantially enhance risk assessment while also providing solutions that ultimately reduce population-level Sb exposure. Given antimony's emergence as a cardiometabolic toxicant prevalent in FCMs, such coordinated action is needed to protect human health and promote health equity.

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The authors declare no competing interests.

Data availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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