La Medicina del Lavoro Med Lav 2011; *102*, 4: 310-320

The IARC Monographs on the carcinogenicity of crystalline silica

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Key words
Silica; carcinogenesis; humans; rodents; IARC

Summary
Background: *Through extensive review of the published literature, two independent expert panels convened by the International Agency for Research on Cancer (IARC) Monographs Programme have classified crystalline silica as carcinogenic to humans while amorphous silica was not classifiable as to its carcinogenicity in humans. The panel remarked that crystalline silica in the form of quartz or cristobalite dust causes lung cancer in humans.* **Objectives:** *We discuss the literature and rationale used to support the IARC evaluations of silica.* ***Methods:*** *A critical review, with a focus on lung tumors, was conducted of the pertinent literature on the carcinogenic effects of crystalline silica in humans and experimental animals as well as supportive mechanistic evidence.* **Results:** *The strongest supportive evidence comes from pooled and meta-analyses that employed quantitative exposure assessment, focused on silicotics, accounted for potential confounding and demonstrated exposure-response trends. Consistency of the effect was observed despite some heterogeneity between individual studies. Tumor site concordance was observed with rodents and further supported by mechanistic data.* **Conclusions:** *Several million workers worldwide are exposed to crystalline silica. Silicosis and lung cancer in these workers are completely preventable diseases. The IARC evaluations are critical to supporting public health interventions to protect persons at high-risk.*

Riassunto
«Le monografie IARC sulla cancerogenicità della silice cristallina». *A seguito di un accurato esame della letteratura, due panel di esperti riuniti dal Programma Monografie dell'Agenzia Internazionale per la Ricerca sul Cancro (IARC), tra loro indipendenti, hanno concordemente classificato la silice cristallina come cancerogena per l'uomo, mentre la silice amorfa è stata considerata non classificabile riguardo alla sua cancerogenicità umana. Nelle loro conclusioni, i panel hanno sottolineato che la silice cristallina, in forma di polveri di quarzo o cristobalite, è causa di neoplasie polmonari nell'uomo. Focalizzando la nostra attenzione sulle neoplasie polmonari, abbiamo condotto un riesame critico della letteratura scientifica sugli effetti cancerogeni della silice cristallina nell'uomo e negli animali da esperimento, nonché sulle evidenze emerse dagli studi sui meccanismi cancerogenetici, e sul percorso razionale utilizzato a supporto delle valutazioni sulla silice espresse dai panel IARC. Il contributo più forte a supporto del ruolo cancerogeno della silice deriva da studi di metanalisi e analisi combinate di dati raccolti in versi studi (pooled) basati su valutazioni quantitative di esposizione, incentrati sui silicotici, che hanno preso in considerazione il ruolo di potenziali confondenti, e hanno dimostrato dei trends in aumento in relazione all'aumento degli indici di esposi-*

Pervenuto il 14.1.2011 - Accettato il 4.4.2011
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zione. È stato inoltre osservato sostanziale accordo tra i risultati, nonostante sia stata rilevata una certa eterogeneità tra i singoli studi. La concordanza esistente con l'organo bersaglio nei roditori e studi sui meccanismi cancerogenetici della silice cristallina hanno fornito ulteriore supporto alla evidenza di cancerogenicità. In tutto il mondo, alcuni milioni di lavoratori sono professionalmente esposti a silice cristallina; in questi lavoratori, sia la silicosi che il tumore polmonare sono malattie del tutto prevenibili. Le valutazioni IARC assumono una valenza determinante per interventi di sanità pubblica allo scopo di proteggere lo stato di salute di persone ad elevato rischio.

History of Evaluations by the IARC Monographs Programme on the Carcinogenicity of Silica

The Monographs Programme of the World Health Organization's (WHO) International Agency for Research on Cancer (IARC) identifies and evaluates potential carcinogenic hazards to humans through critical reviews of the published scientific evidence. IARC has conducted several reviews of the carcinogenicity of crystalline silica (a generic term for several crystalline minerals composed of silica) and amorphous silica (a generic term for various silica forms such as diatomite, diatomaceous earth, fumed silica, fused silica, vitreous silica, silica glass, silica gel, kieselguhr, colloidal silica and precipitated silica) (40-42, 77). The major forms of crystalline silica to which humans have been exposed are quartz, tridymite, cristobalite, with the other forms being very rare (42, 77).

Amorphous silica is generally less toxic and cleared more rapidly from the lung than crystalline silica. To date, there have been no adequate epidemiological data available to evaluate the carcinogenicity of amorphous silica which, together with *inadequate evidence* in experimental animals for the carcinogenicity of uncalcined diatomaceous earth and synthetic amorphous silica, has led to its classification in Group 3, *not classifiable as to its carcinogenicity in humans* (43).

In June 1986 and March 1987 (40, 41), two IARC Working Groups separately concluded that the evidence for the carcinogenicity of crystalline silica was *limited* in humans but *sufficient* in experimental animals. The 1987 evaluation of crystalline silica led to its classification in Group 2A, *probably carcinogenic to humans* (43). An IARC Working Group reviewed additional literature in 1997 (42) and classified crystalline silica in Group 1, *carcinogenic to humans,* which was later re-confirmed in 2010 by a separate IARC Working Group (77). The 1997 evaluation was based on *sufficient evidence* in humans for the carcinogenicity of inhaled crystalline silica in the form of quartz or cristobalite from occupational sources and *sufficient evidence* in experimental animals for the carcinogenicity of quartz and cristobalite (42). The 2010 Working Group affirmation of the Group 1 classification was based on *sufficient* evidence in humans for the carcinogenicity of crystalline silica in the form of quartz or cristobalite and *sufficient* evidence in experimental animals for the carcinogenicity of quartz dust. The Working Group remarked that crystalline silica in the form of quartz or cristobalite dust causes lung cancer in humans.

The lung is the principal target organ of carcinogenicity for crystalline silica and will be the focus of this review of the literature used to reach the IARC evaluations; the epidemiological evidence of associations with other organs sites (e.g. stomach, esophagus, kidney, larynx) is inconsistent or scarce.

Summary of the Epidemiological Evidence on the Lung Carcinogenicity of Crystalline Silica

Quantitative exposure measurements together with evidence of exposure-response relationships support a causal association between crystalline silica exposure and lung cancer risk and also facilitate the interpretation of this association in the presence of potential confounders.

Five main industrial settings are important for assessing the association between crystalline silica exposure and the risk of lung cancer: the ceramics and ore mining industries (in which workers encounter mixed exposures) in addition to sand and gravel operations, quarries, and diatomaceous earth facilities which have the least potential for confounding. Numerous studies have been conducted in these industries, with many demonstrating exposure-response relationships that support a causal association between crystalline silica exposure and lung cancer risk. Some of the studies highlighted by previous IARC Working Groups as being influential in reaching an evaluation have been conducted in gold miners in South Dakota, United States (4, 53, 74); Danish stone industry workers (35); granite shed and quarry workers in Vermont, United States (16, 19); crushed stone industry workers in the United States (15); diatomaceous earth industry workers in the United States (10, 11); refractory brick workers in China (22) and Italy (55, 62, 63); pottery workers in the United Kingdom (5, 13, 52, 85) (14, 51) and China (12, 54) and in cohorts of registered silicotics from North Carolina, United States (1-3) and Finland (59).

Reports from other industries have added further support although the role of crystalline silica exposure in lung cancer risk is less clear due to potential confounding by exposure to arsenic (54), radon (37, 64), or polycyclic aromatic hydrocarbons (PAHs) (86). Mixed findings have been reported among gold (36, 37, 53, 64, 74), tungsten (12, 54), and lead/zinc miners (7). Furthermore, studies of individuals with silicosis, a biomarker of high exposure to silica dust (but also a potential biomarker of susceptibility), are potentially informative for assessing lung cancer risk associated with silica exposure.

Pooled and meta-analyses

The strongest supportive evidence for the carcinogenicity of crystalline silica on the lung comes from pooled and meta-analyses. A pooled analysis (75) demonstrated clear exposure-response, while all of the eight meta-analyses on this topic (27, 48-50, 60, 72, 76, 78) strongly confirmed an overall effect of silica dust exposure, despite some indication of heterogeneity of results between the individual studies (table 1).

Exposure-response analyses

In a pooled dataset of 10 cohorts from various countries and industries (diatomaceous earth, granite, industrial sand, and pottery workers, and tungsten, tin, and gold mines), Steenland et al. (75) conducted a nested case-control analysis employing quantitative estimates of silica exposure. All indices of cumulative silica exposure (cumulative, unlagged and lagged; log cumulative, unlagged and lagged) showed highly significant trends with lung cancer risk ($P<0.0001$); there was also a statistically significant trend ($P<0.05$) with average exposure. Further, there was no strong evidence for heterogeneity across the cohorts when using log cumulative exposure as the exposure metric ($P=0.08$ and 0.34 for unlagged and 15-year lag). Similar results were observed in both mining and non-mining subgroups. Data on smoking were not available in the majority of the individual studies in the pooled dataset, though 5 of the 10 studies previously showed that smoking was not a major confounder. Sensitivity analyses omitting cohorts with other suspected confounders (radon in South African gold mines, and arsenic or PAHs in Chinese tin miners and pottery workers) did not change the overall findings. The most recent IARC Working Group noted that the robustness in these findings indicates that any potential confounding in individual studies likely did not impact the overall results (77).

Lacasse et al. (49) conducted a meta-analysis to examine exposure-response by including 10 studies with quantitative measurements of silica exposure and adjustment for smoking. An increasing risk of lung cancer with increasing cumulative exposure to silica was observed.

Analyses in silicosis patients

There is ongoing discussion if silicosis is a necessary precursor to lung cancer, but this has been very difficult to investigate methodologically. Sev-

Table 1 - Relative risks (95% confidence intervals) from pooled- and meta-analyses of lung cancer among silicotics or silica-exposed workers

Reference	Study design	Silicotics only	Silica-exposed	Silica-exposed without silicosis	Overall
Pooled analysis					
Steenland *et al.* (2001)[d] (75)	Nested case-control				1.06 (1.03-1.09)[e]
Meta-Analyses					
Smith *et al.* (1995)[b] (72)	Overall	2.2 (2.1-2.4)			
	Cohort	2.0 (1.8-2.3)			
	Case-control	2.5 (1.8-3.3)			
Steenland & Stayner (1997)[b] (76)	Overall	2.3 (2.2-2.4)	1.3 (1.2-1.4)		
Tsuda *et al.* (1997)[b] (78)	Overall	2.74 (2.60-2.90)[a]			
		2.76 (2.41-3.16)[b]			
	Cohort	2.78 (2.41-3.22)[b]			
	Case-control	2.79 (2.00-3.89)[b]			
Kurihara & Wada (2004)[b] (48)	Overall	2.37 (1.98-2.04)	1.32 (1.23-1.41)	0.96 (0.81-1.15)	
	Cohort	2.49 (2.08-2.99)	1.29 (1.20-1.40)		
	Case-control	1.89 (1.45-2.48)	1.42 (1.22-1.65)		
Lacasse *et al.* (2005)[b] (50)	Cohort	2.45 (1.63-3.66)			
	Case-control	1.70 (1.15-2.53)			
Pelucchi *et al.* (2006)[b] (60)	Overall	1.74 (1.37-2.22)			
	Cohort	1.69 (1.32-2.16)	1.25 (1.18-1.33)	1.19 (0.87-1.57)	1.34 (1.25-1.45)
	Case-control	3.27 (1.32-8.2)	1.41 (1.18-1.70)	0.97 (0.68-1.38)	1.41 (1.18-1.67)
Erren *et al.* (2009)[b] (27)	Overall	2.1 (2.0-2.3)[a]		1.2 (1.1-1.3)[a]	
		2.1 (1.9-2.3)[b]		1.2 (1.0-1.3)[b]	
		2.1 (1.8-2.4)[c]			
	Cohort	2.1 (1.9-2.2)[a]		1.2 (1.1-1.3)[a]	
	Case-control	2.1 (1.7-2.6)[a]		1.0 (0.7-1.3)[a]	
Lacasse *et al.* (2009)[d] (49)	Overall				1 mg/m^3/year 1.22 (1.01-1.47) 6 mg/m^3/year 1.84 (1.48-2.28)

[a] Fixed effects analysis
[b] Random effects analysis
[c] Fixed effects, adjusted for smoking
[d] Exposure-response analysis
[e] Units of exposure metric: ln(mg/m^3 x years + 1), lagged 15 years

eral meta-analyses have focused on individuals with silicosis (27, 50, 72, 78) while others have focused on individuals without silicosis or of unknown silicosis status (27, 48, 60, 76). Generally, elevated lung cancer risks were observed in analyses among workers with silicosis or silica-exposed

workers. Furthermore, there was consistency in the results across analyses: the summary relative risks ranged from 1.74-2.76 for those with silicosis and 1.25-1.32 for silica-exposed workers. The analyses including only patients without silicosis showed no statistically significant association between crystalline silica exposure and lung cancer risk. However, the IARC Working Group noted that studies that restrict their analysis to individuals without silicosis potentially limit their range of silica exposure which would result in reduced power to detect associations and tend to omit individuals with the highest exposures.

Further comments on potential confounding

Many of the meta-analyses support the findings that crystalline silica exposure is causally associated with lung cancer risk and that the results are not due to potential confounding. For example, an elevated risk of lung cancer was present in non-smokers and persisted after adjusting for smoking (48, 50, 72, 78). Further, results were similar when including both smoking-adjusted and unadjusted studies (27).

In a more detailed analysis, Yu and Tse (87) investigated the potential confounding by smoking on the published results of crystalline silica exposure and risk of lung cancer, and noted that the risks in never smokers had been systematically underestimated. An underestimated SMR/SIR of lung cancer in non-smokers but an overestimation for smokers in a cohort could occur if the age-specific (mortality/incidence) rates of the general population are used for calculating the expected number (of deaths/incident cases) without accounting for smoking habits. In an analysis among never smokers from 10 cohort studies, 2 of the published studies showed significant lung cancer risks. However, when accounting for the smoking habits of the general population and the population specific risk ratios for tobacco smoking and lung cancer, 5 studies reached statistical significance. The SMRs/SIRs for ever smokers were reduced after adjustment for smoking but remained statistically significant in general.

The carcinogenicity of crystalline silica in experimental animals: Routes, species, and sites

Several studies provide clear evidence of the lung carcinogenicity for crystalline silica or quartz after inhalation or intratracheal instillation exposure in rats, but not in mice or hamsters. Further, female rats are more susceptible than males to the induction of lung tumors. The mechanistic basis of these sex and species differences is unknown (42, 77).

Inhalation of crystalline silica or quartz produced a clear exposure-response relationship for induction of lung tumors in rats (table 2). In rats exposed via inhalation to crystalline silica or quartz, increased incidence of adenocarcinomas, squamous cell carcinomas, and adenomas of the lung was observed compared to controls (17, 38, 39, 44, 56-58, 73).

Intratracheal instillation of crystalline silica has been utilized in several rodent studies. In contrast to the instillation studies in mice, lung tumors were induced by intratracheal instillation of crystalline silica or quartz in several studies in rats (table 3). Lung adenocarcinomas in rats were induced by quartz from a single intratracheal instillation of Min-U-Sil or novaculite (34, 66-68) and also by weekly instillations (38, 61). The incidence was greater in exposed animals compared to controls.

Other cancer sites associated with exposure to crystalline silica

Quartz induced lymphomas in rats after intrathoracic, intrapleural and intraperitoneal administration (80-83) and in mice after subcutaneous administration (25). Lymphomas have not been observed in any other species following inhalation exposure to crystalline silica.

Mechanistic evidence for the carcinogenicity of crystalline silica

Crystalline silica is poorly soluble and biopersistent: particles can induce lung inflammation that persists even after cessation of exposure. The car-

Table 2 - Carcinogenicity studies of inhaled crystalline silica or quartz in rats

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start Particle size, GSD[a]	Incidence of tumours in respiratory tract
Rat, Fischer 344 (M, F) 24 months (Dagle *et al.*, 1986) (17)	0, 50 mg/m^3 quartz (Min-U-Sil) 6 hours/day, 5 days/week, 72 rats/sex MMAD[b], 1.7–2.5 μm; GSD, 1.9-2.1	Lung epidermoid carcinomas Males 0/42 (control), 1/47 Females 0/48, 10/53
Rat, Fischer 344 (F) 83 weeks (Holland et al., 1983, 1986; Johnson *et al.*, 1987) (38, 39, 44)	0, 12 mg/m^3 quartz (Min-U-Sil) 6 hours/day, 5 days/week, 62 rats MMAD, 2.24 μm; GSD, 1.75	Lung tumours: 0/54 (control), 18/60 (11 adenocarcinomas, 3 squamous cell carcinomas, 6 adenomas)
Rat, SPF Fischer 344 (M, F) 24 months (Muhle *et al.*, 1989, 1991, 1995) (56-58)	0, 1 mg/m^3 crystalline silicon dioxide (87% cristallinity as quartz) 6 hours/day, 5 days/week, 50 rats/sex MMAD, 1.3 μm; GSD, 1.8	Lung tumours: 0/100 (control M+F), 7/50 (M), 12/50 (F) Males: 1 adenoma, 3 adenocarcinomas, 2 benign cystic keratinizing squamous cell tumours, 1 adenosquamous carcinoma, 1 squamous cell carcinoma Females: 3 adenomas, 8 adenocarcinomas, 2 benign cystic keratinizing squamous cell tumours
Rat, Wistar (F) 29 days (Spiethoff *et al.*, 1992) (73)	0, 6.1, 30.6 mg/m^3 quartz 6 hours/day, 5 days/week, 90 rats MMAD, 1.8 μm; GSD, 2.0	0/85 (control), 37/82 (low dose), 43/82 (high dose) Multiple tumours/rat 21 bronchiolo-alveolar adenomas, 43 bronchiolo-alveolar carcinomas, 67 squamous cell carcinomas, 1 anaplastic carcinoma

[a] GSD, geometric standard deviation
[b] MMAD, mass median aerodynamic diameter

cinogenic potency of crystalline silica may vary depending on a number of factors. Physico-chemical features like the polymorph (a solid material that exists in more than one form or crystal structure) characteristics or the associated contaminants (e.g., trace of iron impurities) may modulate the biological response to silica (26). Particle size, shape, crystallinity, and solubility are other aspects relevant to primary genotoxicity (26, 70). For quartz, the surface properties may vary depending on the origin and its pathogenic potential appears to be related to theses properties. The large variability in potency even within quartz particles of the same polymorph may come from the particle shape, the grinding procedure, the thermal treatment and the metal impurities (30). Several studies showed that freshly ground quartz (e.g. as in sandblasting) is more potent (79) because, immediately after cleavage, a large number of surface active radicals are formed which rapidly decay (18).

Iron coverage of silica particulates inhibits cytotoxicity and cell transformation while iron in traces may enhance the effect (31). Furthermore, the association of DQ12 quartz with aluminum containing compounds (e.g. clay) inhibits most adverse effects (24, 70). Also, *in vitro* and *in vivo* studies on synthesized nano particles of quartz indicate variable effects at the nanoscale (84). Cytotoxicity may also be affected by hydrophilicity, which depends upon the circumstances under which the surface was created. Decreased cytotoxicity has been observed with lowering hydrophilicity (32). For example, sili-

Table 3 - Carcinogenicity studies of intratracheally instilled silica in rats

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start Particle size	Incidence of tumours
Rat, Sprague Dawley Life span (Holland *et al*., 1983) (38)	0, 7 mg quartz (Min-U-Sil) Once a week, for 10 weeks 40 rats MMAD[c], 1.7 μm	0/40 (control), 6/36 (1 adenoma, 5 carcinomas)
Rat, Fischer 344 (M) 22 months (Groth *et al*., 1986) (34)	0, 20 mg quartz (Min-U-Sil) once only 85 rats; MMAD[c], < 5 μm	1/75 (control), 30/67 All adenocarcinomas
Rat, F344/NCr (M, F) 17-26 months (Saffiotti, 1990, 1992; Saffiotti *et al*., 1996) (66-68)	0, 12, 20 mg quartz Once only Ferric oxide (20 mg) was negative control Unspecified number of rats MMAD[c], 0.5–2.0 μm	M: 0/32 (controls); 12 mg, 12/14 (Min-U-Sil 5), 7/9 (HF[d]-etched Min-U-Sil 5) F: 1/20 (controls); 12 mg, 8/9 (Min-U-Sil 5); 8/8 (HF[d]-etched Min-U-Sil 5); 20 mg, 6/8(Min-U-Sil 5) One adenoma in untreated control rat No tumours observed in ferric oxide negative control group
Rat, Wistar Life span (Pott *et al*., 1994) (61)	0, 3 mg one single or 15 weekly injections of one of 3 types of quartz (DQ 12, Min-U-Sil, F 600) Some rats received PVNO[b] to protect against silicosis 37–50 rats/group; MMAD[c] not specified	adenoma; adenocarcinoma; benign cyctic keratininzing squamous cell tumors, and [e]other types of tumours in the lung

[a] Sex not specified
[b] PVNO, polyvinylpyridine N-oxide
[c] MMAD, mass median aerodynamic diameter
[d] Hydrogen fluoride
[e] Other types of tumours in the lung: fibrosarcoma, lymphosarcoma, mesothelioma or lung metastases from tumours at other sites

ca that is generated at high temperature in fly ashes or volcanic dusts is mostly hydrophobic.

Three mechanisms have been proposed by the IARC Working Group regarding the carcinogenicity of crystalline silica in rats:

1. The persistence of crystalline silica in the lung increases if exposure impairs macrophage-mediated particle clearance, resulting in macrophage activation, and sustained release of chemokines and cytokines. Mineral dusts bind to a variety of cell surface receptors expressed by macrophages and this induces phagocytosis, macrophage apoptosis, or macrophage activation. The pathological consequence of silica-induced injury to alveolar macrophages, followed by apoptosis is impaired alveolar macrophage-mediated clearance of crystalline silica (42, 77).

2. Epithelial cell proliferation may result from an extracellular generation of free radicals by crystalline silica and the depletion of antioxidants in the lung lining fluid. Reactive oxygen species are generated not only at the particle surface of crystalline silica, but also by phagocytic cells and epithelial cells exposed to quartz particles (9, 20) that

can directly induce DNA damage (33, 46, 71). Lung injury may be initiated and amplified by severe inflammation (8, 21, 47). Persistent inflammation triggered by crystalline silica (quartz) has been linked to indirect genotoxicity in lung epithelial cells in rats (42, 77). These rats develop a severe, prolonged inflammatory response characterized by elevated neutrophils, epithelial cell proliferation, and development of lung tumors (23). In the presence of quartz, the ascorbic acid and glutathione are used via two respective reactions that may deplete antioxidant defenses in the lung lining fluid, enhancing the extent of oxidative damage (28, 29).

3. Crystalline silica particles are taken up by epithelial cells that cause intracellular generation of free radicals and then induce genotoxicity. The relationship between DNA strand-break formation and uptake of quartz particles was investigated *in vitro* with A549 human lung cells: DNA strand-breaks measured in the exposed cells were highly correlated with the number of particles ingested by the cells as well as with reactive oxygen species generation (69). Other *in vitro* studies using different quartz species observed DNA strand breaks only at cytotoxic particle concentrations (6)

It is unknown which of these mechanisms occur in humans exposed to crystalline silica dust. The IARC Working Group considered the first mechanism as the most prominent based on the current experimental data in rats using inhalation and intratracheal instillation, without excluding the other mechanisms. The mechanism responsible for induction of lymphomas in rats and mice following direct injections of crystalline silica dust is unknown (77).

Conclusion

The most recent IARC Working Group confirmed the carcinogenicity of crystalline silica (77). Although there has been some heterogeneity across studies and across industries, an increased risk of lung cancer following crystalline silica exposure has been demonstrated in pooled- and meta-analyses using quantitative exposure assessment supported by consistency across studies and exposure-response trends. This increased risk in humans is supported by tumor site concordance with carcinogenesis studies in rodents and additional mechanistic support, although it is not clear which mechanism predominates.

Global estimates of exposure to crystalline silica and silica-related lung cancer are not directly available. For the European Union, it has been estimated that approximately 3.2 million workers in the European Union were occupationally exposed to crystalline silica in the early 1990s (45) and a recent estimate of the burden of occupational cancer in the UK found that silica, after asbestos, was the second most important lung carcinogen (65). Silicosis and lung cancer resulting from occupational exposure to crystalline silica are completely preventable diseases. Therefore in 1995, the International Labour Organization and the WHO jointly started a global effort to eliminate silicosis by 2030.

No potential conflict of interest relevant to this article was reported

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