COD
Contact Dermatitis

Chromium in leather footwear – risk assessment of chromium allergy and dermatitis

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doi:10.1111/j.1600-0536.2012.02053.x

Summary

Background. Chromium-tanned leather footwear, which releases > 3 ppm hexavalent Cr(VI), may pose a risk of sensitizing and eliciting allergic dermatitis.
Objectives. To determine the content and potential release of chromium in leather footwear and to discuss the prevention of chromium contact allergy and dermatitis.
Methods. Sixty pairs of leather shoes, sandals and boots (20 children's, 20 men's, and 20 women's) were purchased in Copenhagen and examined with X-ray fluorescence spectroscopy. Chromium was extracted according to the International Standard, ISO 17075. The detection level for Cr(VI) was 3 ppm.
Results. Chromium was identified in 95% of leather footwear products, the median content being 1.7% (range 0–3.3%). No association with store category or footwear category was found. A tendency for there to be a higher chromium content in footwear with high prices was shown ($p_{\text{trend}} = 0.001$). Cr(VI) was extracted from 44% of 18 footwear products, and, in three items, more than 10 ppm was extracted. One shoe had 62 ppm Cr(VI) extracted. Sandals seemed to be over-represented among footwear with detectable Cr(VI). Cr(III) extraction reached a median value of 152 ppm.
Conclusions. Most leather footwear contained chromium. Cr(VI) was extracted from a high proportion of leather footwear; this poses a risk of sensitization.

Key words: allergic chromium dermatitis; chromium allergy; content; exposure; leather; release.

Leather is most often tanned with trivalent chromium [Cr(III)] sulfate to obtain softness, durability, and flexibility (1). Cr(III) stabilizes certain proteins, which makes the leather resistant to degradation. Hexavalent chromium [Cr(VI)] is not used for leather tanning, but can occur as an impurity (1). Cr(III) salts can be converted into Cr(VI) compounds when, for example, high pH or light and heat combined with the presence of oxidized fat provoke the oxidization of Cr(III) to Cr(VI) (2). Most Cr(III) is tightly bound to collagen fibres in the leather, but a surplus of Cr(III) can be released from the leather during use and cause contact sensitization. Patients with contact allergy to both Cr(III) and Cr(VI) have a higher prevalence of foot dermatitis than patients reacting only to Cr(VI) (3). However, Cr(VI) is regarded as a far more potent sensitizer than Cr(III), as it can easily penetrate the epidermis (4), whereas Cr(III) tends to form stable complexes, preventing penetration (5, 6). For this reason, Cr(VI) is considered to be the main culprit. Experimental studies have determined the threshold level for elicitation of chromium-allergic dermatitis. One study showed that the patch test threshold

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Conflicts of interest: The authors have no conflict of interest to disclose. Funding: The Leo Pharma Research Foundation, The Else and Mogens Wedell-Wedellsborgs Foundation, a Gerhard Brøndsteds travel grant and the Danish physicians insurance under Codan/SEB Pension are thanked for their unrestricted financial support of Jacob Thyssen's salary.

Accepted for publication 26 November 2011

was 10 ppm when 17 chromium-allergic patients were patch-tested on normal skin, and that the presence of an irritant lowered the threshold level to only 1 ppm in two patients (7).

From a clinical point of view, chromium-allergic dermatitis is often severe, resulting in a prolonged course of disease as compared with other contact allergies (8). We recently showed that 55% of 197 Danish chromium-allergic dermatitis patients patch tested between 1995 and 2007 had relevant leather exposure at some point (9). Exposure to leather footwear was more frequent in females than in males (39% versus 27.9%), and nearly half of the chromium-allergic patients had foot dermatitis. Importantly, we found a significant increase in chromium allergy between 1995 and 2007, mainly caused by leather exposure. Also, we showed an increase in strong patch test reactivity (defined as 2+ and 3+ reactivity) to chromium in Danish dermatitis patients in recent years (10). On the basis of the above findings, it was interesting to investigate the content of chromium in footwear purchased in Denmark. We report the main findings from a study on chromium in leather that was recently performed in Copenhagen and led by an initiative from the Danish Environmental Protection Agency (DEPA) (http://www.mst.dk/English/Chemicals/Consumer_Products/Allergy_provoking_substances_in_leather_goods.htm). The present article, however, does not report any statements from the DEPA, but is based on the author's opinions and interpretation.

Materials and Methods

Footwear samples

Sixty pairs of leather shoes, sandals and boots (20 children's, 20 men's, and 20 women's) were purchased from well-known shoe stores in Denmark, as well as from stores with independent ownership, supermarkets, and sport shops. This was done to obtain a sample of leather footwear that fairly represented the market in Denmark. All purchases were made in the Greater Copenhagen area during September to October 2009. Only footwear with leather components in contact with the skin was purchased. Thus, shoes with, for instance, padding were not bought. We aimed at buying footwear that typically would be worn with bare feet (e.g. sandals and stilettos), shoes that could be used during sport activities, resulting in increased perspiration, and footwear with a large surface area in contact with the skin, such as boots. The categories of footwear that were purchased are shown in Table 1. Prices varied between 75 and 3000 DKK (∼ €10–390), and the numbers purchased are shown in Table 2. The average price per pair of purchased footwear was 554 DKK (€72). In 28 cases, it was possible to retrieve data regarding the country of manufacture. The countries included Italy (10), China (4), Portugal (3), Spain (2), Denmark (2), other Asian countries not defined (2), France (1), Belgium (1), Mexico (1), Germany (1), and India (1).

Table 1. Footwear purchased in Copenhagen in 2009 stratified by category

	Children's	Women's	Men's	Total
Shoes	13	3	16	32
Boots	4	7	3	14
Sandals	3	10	1	14
Total	20	20	20	60

Chromium content analysis

The chromium content of the footwear sample was assessed with an X-ray fluorescence (XRF) instrument [Niton XLt 797Z (s/n 12338); Holger Andreasson AB, Örebro, Sweden]. The results obtained with XRF screening indicate which elements are present and their approximate proportional distribution. This semiquantitative screening method may therefore indicate whether or not the element in question is present. The level of detection is estimated to be 0.01% (based on a calibration procedure for restriction of hazardous substances screening of materials with the integrated Plastic Analyser Mode software). Thus, samples that showed a content of chromium below this value (reported as below the level of detection) cannot be assumed with certainty not to contain chromium. As most shoes and boots had an inner sole consisting of a different type of leather from the leather used to make the shoe or boot itself, each piece of footwear was scanned at two different places: (i) the sole (from inside the shoe); and (ii) the part constituting the shoe (also from the inside). In some cases, it was necessary to cut up the shoe to perform a proper screening. Some of the shoes may have contained several other leather pieces, which were not analysed. The risk of false-negative results from tested parts is assumed to be insignificant; however, the possibility that this occurred at very low levels cannot be ruled out. Finally, the results do not offer any information about which form [Cr(VI) or Cr(III)] of the element was present.

Chromium extraction analysis

A total of 18 pairs of footwear were analysed for potential chromium release. Selection was based on store category, footwear category, price range, and the outcome of XRF analysis performed on the leather parts used to create the shoe, sandal or boot itself. We aimed at testing footwear

Table 2. Purchased footwear stratified by price and chromium content as established by X-ray fluorescence analysis

	No. of shoes purchased					
	3	21	17	11	3	5
Price range (DKK)	75–200	200–400	400–600	600–800	800–1000	1000–3000
Price range (€)	10–26	26–52	52–78	78–104	104–130	130–390
Average chromium content (%)	0.9	1.8	1.6	1.7	2.1	2.3

from each category to ensure that all were equally presented. As well as footwear manufactured in Portugal, Italy, Mexico, France, and India, we also included footwear from unknown sources. Most were bought from shoe stores, but footwear from clothing stores and malls were also included. Extraction of Cr(VI) was performed according to the International ISO Standard, ISO 17075, which measures the mass fraction expressed in milligrams per kilogram of soluble Cr(VI) in leather. Briefly, soluble Cr(VI) was leached from the sample in a phosphate buffer at pH 7.5–8.0, and substances that might influence the determination were removed by solid-phase extraction. When Cr(VI) is present in the solution, 1,5-diphenylcarbazide is oxidized to 1,5-diphenylcarbazone and forms a red–violet complex with chromium, which can be quantified photometrically at 540 nm. The method is suitable for quantification of Cr(VI) extraction from all leather types down to a concentration of 3 ppm. The results may be regarded as measurements of total potential skin exposure to chromium [Cr(VI) and Cr(III)] from leather. The Cr(III) content was determined by performing an analysis [by inductively coupled plasma optical emission spectrometry (ICP-OES)] of the total chromium content in the extraction solution used for determining the Cr(VI) content and then subtracting the value for the Cr(VI) content. This is possible because of the generally accepted assumption that chromium is only present as elemental Cr(III) and Cr(VI). All results are presented as mg Cr(III)/kg (ppm) leather.

Chemicals required in ISO 17075

1,5-Diphenylcarbazide (CAS 140-22-7), potassium hydrogenphosphate.$3H_2O$ (CAS 16788-57-1), potassium dichromate (CAS 7778-50-9), and acetone (CAS 67-64-1), all were from Merck (NJ, USA). Orthophosphoric acid (CAS 7664-38-2) was from BDH (Poole Dorset, the UK) . SPE cartridges were SEP-PAK C18 from Waters (Milford, MA, USA), typically 1 g, except for the very strongly coloured extracts, where 5 g cartridges were used.

Instrumentation

Colometric measurements were performed with a Lambda-2 UV-VIS spectrophotometer (Perkin-Elmer, Rodgau, Germany). ICP-OES measurements were performed on a model ICAP 6500 from Thermo Scientific (USA).

Statistical analysis

The chi-square linear trend test was used to test for differences across strata. Data analyses were performed with SPSS (IBM, Armonk, NY, USA) for Windows™ (release 20.0).

Results

Chromium content

XRF screening of purchased footwear showed a pattern reminiscent of the normal distribution (Fig. 1). The median chromium content was 1.7% (range 0–3.3%). No difference was found between leather parts used to make the footwear itself and the inner soles. Hence, the median chromium contents were, respectively, 1.7% (range 0.1–3.3%) and 1.6% (range 0–3.0%). Furthermore, no association was found between the content of chromium and store category, footwear category (sandals, shoes, or boots), or the group that the footwear was intended for (women's, men's, or children's). However, there was a tendency for there to be a higher chromium content in footwear with high prices than in footwear with lower prices ($p_{\text{trend}} = 0.001$). Three of 60 leather soles had no measurable chromium content at all, whereas chromium was detected in all investigated leather parts in the shoe itself.

Chromium extraction

Chromium extraction measurements for 18 different footwear items, made with the ISO 17075 standard, showed that eight (44.4%) potentially released Cr(VI) in an amount equal to or above the determination limit of 3 ppm (Table 4). In three (16.7%) of 18 footwear items, more than 10 ppm chromium was extracted. The highest extraction value of Cr(VI) was 62 ppm, for a white leather shoe intended for men. Of the eight different footwear items from which Cr(VI) was extracted, four were intended for women, three for men, and one for children.

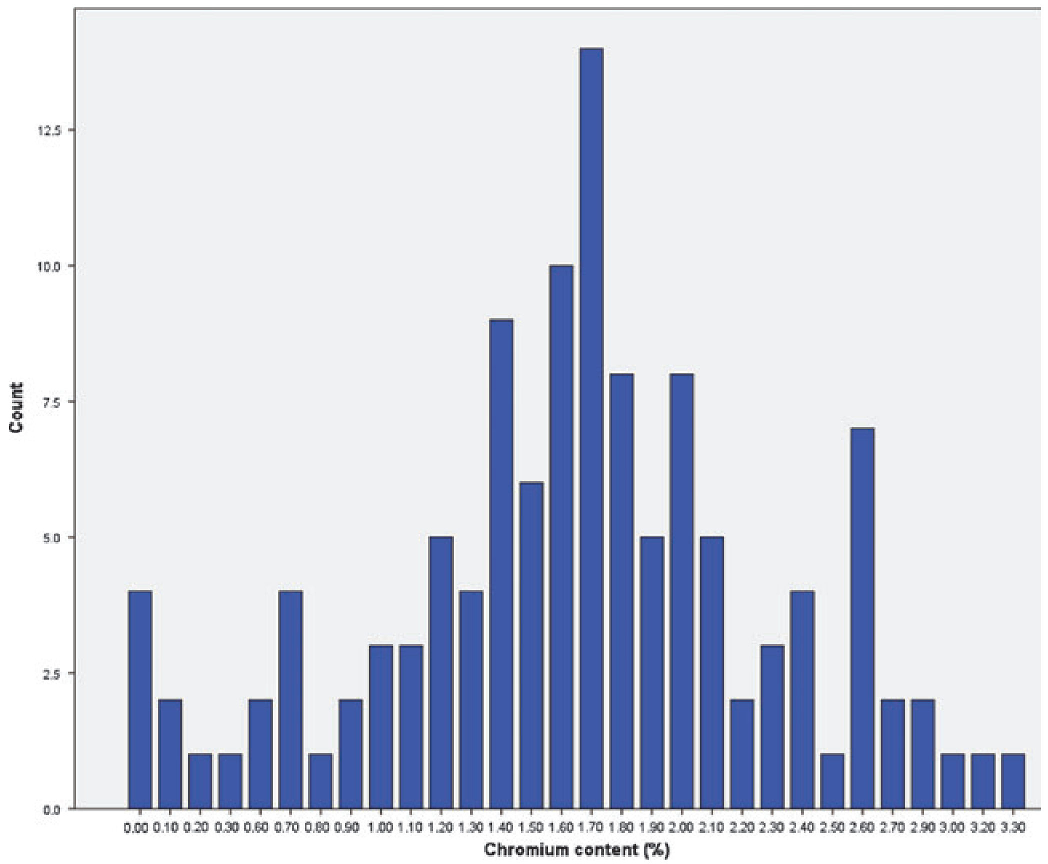

Fig. 1. The chromium content, as assessed by X-ray fluorescence analysis, in 60 different leather footwear products purchased in Copenhagen during 2009.

Table 3. The content of chromium in leather parts and inner soles from 60 different footwear items purchased in Copenhagen stores during 2009 and investigated with X-ray fluorescence analysis

	Chromium content (%)					
	0%	0–1%	1–2%	2–3%	3–3.3%	Total
Leather parts used to make the footwear itself						
Women's	0	4	9	7	0	20
Men's	0	2	10	8	0	20
Children's	0	2	8	8	2	20
Total	0	8	27	23	2	60
Leather inner soles from footwear						
Women's	1	1	15	3	0	20
Men's	0	0	13	6	1	20
Children's	2	4	12	2	0	20
Total	3	5	40	11	1	60
Footwear category						
Shoes	0	4	14	13	1	32
Sandals	0	4	8	2	0	14
Boots	0	0	7	6	1	14
Total no. of footwear items	0	8	29	21	2	60

Table 4. Extraction of chromium [Cr(III) and Cr(VI)] from 18 different footwear items as analysed to ISO 17075

Total [mg/kg (ppm)]	Cr(VI) [mg/kg (ppm)]	Cr(III) [mg/kg (ppm)]	Footwear category
<1	<1	<1	Men's–boot
1	<1	1	Men's–shoe
3	<1	3	Children's–shoe
147	<1	147	Children's–boot
157	<1	157	Men's–boot
159	<1	159	Children's–sandal
164	<1	163	Women's–shoe
218	<1	218	Children's–shoe
233	<1	233	Children's–shoe
277	<1.5	276	Women's–boot
125	3	122	Women's–boot
246	4	242	Women's–sandal
307	4	303	Women's–sandal
42	6	36	Men's–shoe
203	6	197	Women's–sandal
73	16	57	Men's–sandal
98	62	36	Men's–shoe
156	33	123	Children's–sandal

Sandals seemed to be over-represented among footwear with detectable Cr(VI). In general, high extraction levels of Cr(III) were identified. Hence, the median Cr(III) extraction level was 152 ppm (0–303 ppm). Only from one item could we not extract Cr(III).

Discussion

Chromium was identified in 95% of 60 pairs of leather footwear intended for men, women, and children. The median chromium content as assessed by XRF analysis was 1.7%. From three (16.7%) of 18 pairs, more than 10 ppm Cr(VI) was extracted, and from one shoe, 62 ppm Cr(VI) was extracted. In general, Cr(III) extraction was frequent and occurred at a high level, reaching a median value of 152 ppm. When evaluating the risk of chromium sensitization and elicitation of chromium-allergic dermatitis following exposure to leather products from this sample, one needs to consider the high complexity of chromium as a hapten. Indeed, chromium may fluctuate between the hexavalent and trivalent state, depending on factors such as temperature and pH. Cr(III) is typically tightly bound to the collagen in leather, whereas Cr(VI), a poor protein binder, is free. Cr(VI) may therefore be released from leather products, if present, whereas the release of Cr(III) is suspected to mainly derive from a pool of excess Cr(III) resulting from insufficient removal during washing of the finished leather product (2). One study showed that tannery workers who were exposed to Cr(III) developed chromium-allergic dermatitis, emphasizing that the trivalent form of chromium may also cause sensitization (11). Human and animal studies have shown that Cr(VI) may consistently be considered to be stronger contact sensitizer and elicitor of allergic contact dermatitis than Cr(III) (12–16). This is explained by higher bioavailability of Cr(VI), as it is more water-soluble than Cr(III) (15), penetrates the skin more easily (4, 6, 17), and accumulates in the skin to a higher degree than Cr(III) (6, 18). Once inside the skin, Cr(III) binds more easily to proteins than Cr(VI), potentiating antigen presentation and elicitation of chromium-allergic dermatitis (19). Hence, Cr(VI) is converted to Cr(III) inside the skin, as non-protein-bound chromium ions cannot elicit a T cell response. It should be underscored that, for example, nickel can activate the T cells through several different mechanisms, some of which are peptide-independent, and that it is currently unknown whether chromium can also have such effects.

The results should be interpreted in the context of dose–response elicitation data. One of 14 chromium-allergic patients reacted to ~1 ppm Cr(VI) under occlusion (20), whereas the patch test threshold was 10 ppm when 17 chromium-allergic patients were patch-tested on normal skin (7). In the presence of an irritant, the threshold level was reduced to 1 ppm in 2 of 17 patients. Stern et al. gathered nine patch test studies on the elicitation threshold levels for Cr(VI) at different pH levels, and found that 10% reacted to 15 ppm and 5% reacted to 7.6 ppm (21). A review article showed that exposure to occluded patch test concentrations of 7–45 ppm Cr(VI) elicited allergic contact dermatitis in 10% of chromium-allergic patients. The eliciting capacity of Cr(III) has not been systematically investigated, but it is generally agreed that much higher concentrations of Cr(III) than of Cr(VI) are needed to elicit dermatitis (15). In a study by Nethercott et al., only 1 of 54 patients reacted to Cr(III), corresponding to a threshold concentration of 1099 ppm, whereas the estimated minimal elicitation threshold $(MET)_{10\%}$ for Cr(III) was 6 ppm in a more recent study from Denmark (22). An Indian study found no elicitation of chromium-allergic dermatitis in 18 chromium-allergic individuals exposed to 50 ppm Cr(III) (23). Taken together, these findings show that Cr(VI) is a much more potent allergen than Cr(III).

So how do we assess the risk of morbidity following contact with the footwear sample from this study, taking the information on chromium sensitization and dose–response studies into account? There seems to be no risk model yet that can sufficiently combine the scientific insights into the delivery, penetration and activation of the immune system with the content and release of chromium from leather products. Such models should be very detailed and include exact measurements of chromium release, measurement of the concentration of chromium in human sweat, and finally measurement of the chromium content in the skin. For this reason, we need to include clinical considerations in the interpretation, to make it more operative: Cr(VI) is the main culprit, being the strong sensitizer, whereas Cr(III) seems rather to be an elicitor of chromium-allergic dermatitis in already sensitized individuals. Hence, the eight footwear items from which more than 3 ppm Cr(VI) were extracted may indeed pose a risk of sensitization [sensitization would mainly be suspected from the footwear with high Cr(VI) release] and elicitation of chromium-allergic dermatitis, provided that the Cr(VI) is released under use conditions. On the other hand, footwear with the highest Cr(III) release may infrequently result in sensitization, but may rather result in elicitation of chromium-allergic dermatitis. Our study did not consider the amount of bio-available chromium. Hence, chromium ions released from tanned leather shoes (but not sandals) need to pass through both the shoe lining and the socks (if such are used) before they come into direct contact with the skin. In some situations, the level of bio-available chromium may be insufficient to sensitize and elicit dermatitis. Moreover, low pH in human sweat may convert Cr(VI) to Cr(III), again limiting the risk of penetration and contact sensitization. In line with these considerations, the chromium problem is relatively small at a general population level. However, it should be remembered that chromium allergy and dermatitis are relatively frequent in patch tested dermatitis patients, and that dermatologists often see patients with foot dermatitis caused by chromium release from leather footwear, making our findings noteworthy.

There was no association between the content of chromium and store category, footwear category (sandals, shoes, and boots), or the group that the footwear was intended for (women's, men's, or children's). These results indicate that all consumers wearing leather footwear may be exposed to chromium. A high level of Cr(VI) extraction was found from five sandals: 4, 4, 6, 16 and 33 ppm, respectively. Hence, 62.5% of footwear items with detectable Cr(VI) extraction were sandals, despite the fact that the different categories of footwear were evenly selected for analysis. It is perceived that skin exposure to chromium released from leather is more intense if shoes are worn with bare feet and under humid conditions, for example in summer. The significance of this may be appreciated by the fact that chromium allergy and foot dermatitis are highly prevalent in, for example, Africa and India, where warm weather results in frequent use of sandals (24, 25). The present study also showed that a higher chromium content was found in more expensive footwear than in inexpensive footwear. This may be explained by the use of better leather quality in expensive shoes, resulting in softer, more durable and flexible leather products, but also products that contain more chromium. No relationship between the total content of chromium and the release of Cr(VI) was found.

Extraction of Cr(VI) was also evaluated in a sample of leather goods in Denmark in 2002 (15), being, respectively, 6 and 10 ppm from the two shoes that released Cr. In Germany, an investigation performed by the German Risk Assessment Institute, including more than 850 leather consumer items such as gloves and shoes, showed that about half of the items released Cr(VI) above the analytical determination limit (3 ppm), and that one-sixth released more than 10 ppm Cr(VI) (http://www.bfr.bund.de/cd/9575). The Swedish Society for Nature Conservation recently tested 21 pairs of leather shoes from all over the world for the content of different heavy metals and organic compounds (http://www.naturskyddsforeningen.se/upload/press/badshoes.pdf). Most of the chemical compounds studied were assumed to originate from tanning, preservation or dyeing of the leather. Metals in various concentrations were found in all of the shoes. Most of 19 shoes had a total chromium content ranging between 1% and 3%. No detectable levels of Cr(VI) were found, whereas very high levels of Cr(III) were found in shoes, ranging from 42 to 29 000 ppm. Taken together, the levels found in the present study are comparable with results from other surveys, making them reliable. Leather can be produced without leachable Cr(VI), and without affecting the performance of the leather. Three pairs of footwear had low levels of both Cr(VI) and Cr(III), indicating that it is indeed technically possible to produce tanned leather without high levels of Cr and consequently a risk of chromium allergy. The leather industry should strive to change its tanning process to reduce chromium levels in the finished product.

There is currently no regulation of the level of chromium released from leather goods in the EU. However, in July 2007, the German Risk Assessment Institute (Bundesinstitut für Risikobewertung) recommended restriction of the use of chromium salts in leather production as far as possible, or technical reduction of their concentrations during processing to such an extent that Cr(VI) can no longer be detected in the end product (i.e. 3 ppm with current methods) (http://www.bfr.bund.de/cd/9575). The 18th Amendment of the German Consumer Goods Ordinance came into effect on 13 August 2010. This regulation restricts the content of Cr(VI) in leather products to not more than 3 ppm (detection threshold). Epidemiological data from Denmark suggest that chromium allergy and dermatitis have increased in recent years, mainly as a result of leather exposure (9, 26). As leather tanning can be performed without the finished product containing chromium, industry should strongly consider changing production methods, and regulators should consider regulatory interventions to limit chromium exposure from leather footwear. It has been shown in the past that, when contact allergens are removed from products, for example thimerosal from vaccines (27), nickel from metallic consumer items (28), and Cr(VI) from cement (29), the prevalence of that contact allergy decreases. One could consider restricting Cr(VI) to 3 ppm in finished leather footwear (as in Germany) to prevent sensitization, but also making labelling of the Cr(III) content mandatory, to offer already sensitized individuals an opportunity to avoid footwear that may elicit chromium dermatitis.

Acknowledgements

We wish to thank the DEPA for sharing their data.

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