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Increased levels of renal damage biomarkers caused by excess exposure to trivalent chromium in workers in tanneries

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ABSTRACT

Background: The process for leather material production is carried out in developing countries using a large amount of trivalent chromium [Cr(III)]. Assesment of health risks for millions of workers in tanneries worldwide that are highly polluted with Cr(III) is needed.
Methods: Levels of total Cr and its chemical species in wastewater samples from tannery built-up areas of Bangladesh were investigated. Cr-mediated renal damage was assessed in 100 male tannery workers by epidemiological analysis consisting of questionnaires and measurements of levels of urinary Cr and urinary renal damage markers [urinary levels of total protein and kidney injury molecule-1 (KIM-1)].
Results: High levels of total Cr (mean ± standard deviation = 1,908,762 ± 703,450 μg/L) were detected in wastewater samples from 13 sites of tanneries. More than 99.99% of total Cr in the wastewater was Cr(III), indicating that workers in the tanneries were exposed to large concentrations of Cr(III). Cr levels (mean ± standard, 2.89 ± 4.23 μg/g creatinine) in urine samples from the workers in tanneries were > 24-fold higher than the levels in a general population previously reported. Multivariate analysis showed significant correlations between urinary levels of Cr and urinary levels of renal damage biomarkers. Nagelkerke Pseudo R^2 values also showed that Cr level is the strongest contributor to the levels of renal damage biomarkers in the workers.
Conclusion: Our results newly suggest that excess exposure to Cr(III) could be a risk for renal damage in humans.

1. Introduction

Various leather products are used in daily life worldwide. In the processing cycle in leather industries, the tanning stage, which causes environmental pollution, has been off-loaded onto developing countries, while the processing stage, which has a limited environmental burden, is carried out in developed countries (Joseph and Nithya, 2009; Yoshinaga et al., 2018). Thus, tannery-oriented health risks for workers and tannery-oriented environmental pollution based on the unfair allotment of roles in developed and developing countries have become global issues.

Heavy environmental pollution of chromium (Cr) derived from the tanning stage in leather industries has been found in many countries in previous studies (Belay, 2010; Dixit et al., 2015; Yoshinaga et al., 2018; Al Hossain et al., 2019). However, there have been very few studies on the health risk that is correlated with life span for millions of tannery workers worldwide, despite the fact that 90% of tannery workers die before 50 years of age (Maurice, 2001). Assessment of the health risk for tannery workers from contamination in tanneries is needed for the establishment of countermeasures in developing countries.

Cr is an ordinary element in the environment (Yoshinaga et al., 2018). Trivalent chromium [Cr(III)] and hexavalent chromium [Cr(VI)] are well known as chemical species of Cr. Cr(VI)-mediated visual, cutaneous and renal impairments and carcinogenic toxicity have been found in previous *in vitro* and *in vivo* studies (ATSDR, 2012; Ohgami et al., 2015). On the other hand, toxicities of Cr(III) are generally thought to be lower than those of Cr(VI), and Cr(III)-mediated health disturbances have been reported in only a few *in vitro* and *in vivo*

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studies.

Compounds including Cr(III) represented by basic chromium sulfate (BCS) have been used in the tanning process in tanneries worldwide (Thanikaivelan et al., 2005). Most of the 500 million kg of BCS that is produced worldwide every year is used in the tanning process in tanneries (WHO, 2009). A previous study showed that Cr(VI) levels of the air in tanneries was undetectably low (Randall and Gibson et al., 1987). Therefore, there is a possibility that tannery workers are exposed to Cr (III) inside the tanneries. Previous animal studies showed that exposure to Cr(III) resulted in functional damage of the kidneys with histopathological changes (Mathur et al., 1977; Tandon et al., 1978; Fatima et al., 2016), suggesting Cr(III)-mediated renal toxicity. To our knowledge, however, renal toxicity of Cr(III) in humans has not been epidemiologically assessed.

Urine total protein-to-creatinine ratio (UPCR) and urine kidney injury marker-1 (KIM-1) are well-established biomarkers for glomerular and tubular damage in the kidney (D'amico and Bazzi, 2003) and for tubular damage in the kidney (Han et al., 2002), respectively. UPCR exceeding 500 mg/g of creatinine increases the risks of renal failure and mortality (KDIGO, 2012; Nitsch et al., 2013). The upper limit of urinary KIM-1 in healthy subjects has been reported to be 0.27 μg/g creatinine (Seo et al., 2013).

We hypothesized that renal damage caused by exposure to large concentrations of Cr(III) in tanneries could be one of the factors that are involved in the short life span of tannery workers, because renal function is closely related to life span in humans (Wen et al., 2008). We designed an epidemiological study to assess renal damage in tannery workers by using the urinary biomarkers UPCR and KIM-1.

2. Materials and methods

2.1. Environmental monitoring in tanneries

Wastewater samples of pre-tanning, tanning and post-tanning processes were collected at 13 sites of 10 tanneries in tannery built-up areas of Bangladesh. Inductively coupled plasma mass spectrometry (ICP-MS) (Agilent 7500cx) was used for measurement of total Cr in the wastewater (Kato et al., 2016). Levels of Cr(VI) in the wastewater samples were measured by the diphenylcarbazide method.

2.2. Epidemiological study for tannery workers

Information on age, sex, current status of smoking, height, weight and duration of work in a tannery was obtained by self-reported questionnaires, and urine samples were obtained from Bangladeshi male tannery workers (n = 100) following the methods previously reported (Yoshinaga et al., 2018; Al Hossain et al., 2019). Most Bangladeshi people are Muslim, for whom alcohol consumption is prohibited. Therefore, there was also no alcohol consumers in the participants as in the case of previous Bangladeshi studies (Ohgami et al., 2016; Al Hossain et al., 2019; Kato et al., 2020). Levels of total protein and KIM-1 in urine samples of tannery workers were measured by using a pyrogallol red-molybdate protein assay kit (Wako Pure Chemical Industries, Ltd, Osaka, Japan) and a quantitative sandwich ELISA kit (R&D Systems, MN, USA), respectively. After the levels of Cr, total protein and KIM-1 in urine samples had been normalized by urinary creatinine levels (Ruggenenti et al., 1998; Han et al., 2002; Kato et al., 2013), the values were used for statistical analysis. No normal distribution of Cr levels normalized by urinary creatinine levels was exhibited by the Shapiro Wilk test.

2.3. Ethical permission

Our epidemiological study including environmental monitoring was authorized by ethical committees in Nagoya University (2013–0070 and 2016–0036) and in University of Dhaka (5509/Bio.Sc). Permission for environmental monitoring in tanneries and free health examinations for tannery workers was obtained from the Bangladesh Tanners Association (11,772). Informed consent in writing with authorization to disclose health information and photographs was obtained from all of the subjects. Ethical rules for research including humans were always ensured (WMA, 2013).

2.4. Statistical analysis

The average of Cr concentrations (μg/g creatinine) in urine samples was used as a cut-off value. The cut-off values of UPCR (500 mg/g creatinine) and KIM-1 (0.27 μg/g creatinine) were determined according to the guidelines of Kidney Disease Improving Global Outcomes (KDIGO) (2012) and a previous report (Seo et al., 2013), respectively. Age, BMI and smoking were selected as cofounding factors in multivariate analyses because they have been shown in a previous study to affect renal function (Whaley-Connell et al., 2008). Nagelkerke pseudo R^2 values were used to estimate the relative contributions of each variable to biomarker levels for renal damage (UPCR and KIM-1) as shown previously (Nagelkerke, 1991; Li et al., 2018). Statistical analyses were carried out using version 3.4.3 of R software. A difference of < 0.05 was judged as significant.

3. Results

3.1. Cr levels in tannery wastewater samples

The leather manufacturing process can be divided into pre-tanning (Fig. 1A), tanning (Fig. 1B) and post-tanning (Fig. 1C) processes. Since the low cost of a Cr tanning system has a great benefit for both developed and developing countries, > 90% of leather worldwide is produced by the tanning system using Cr(III) (Sundar et al., 2002). In order to identify the Cr species that workers are directly exposed to at the inside tanneries, we measured levels of total Cr and Cr(VI) in the wastewater of tanneries. The average concentrations of total Cr in 13 wastewater samples in the processes of pre-tanning, tanning and post-tanning were 376 μg/L (range: 19–1010 μg/L), 1,908,762 μg/L (range: 929,955–2,763,599 μg/L) and 282 μg/L (range: 91–537 μg/L), respectively (Fig. 1A–D). Cr(VI) levels in all wastewater samples in the pre-tanning process were undetectably low (Fig. 1A, D). Cr(VI) levels in all wastewater samples in the post-tanning process could not be measured due to their dark colors, though average concentrations of total Cr levels in wastewater samples in the post-tanning process were < 0.015% of those in the tanning process. The average of Cr(VI) concentrations was < 50 μg/L (range: 0–106 μg/L) even in wastewater samples from the tanning process (Fig. 1B, D). These results suggest that > 99.99% of Cr species in the wastewater was Cr(III).

3.2. Basic characteristics of the participants

The basic characteristics of the 100 male tannery workers, including 41 smokers, in Bangladesh are shown in Table 1. The proportion of subjects with UPCR levels exceeding 200 mg/g creatinine was shown in a previous study to be only 2.4% of a general population of 11,247 people (non-tannery workers) (Chadban et al., 2003). However, the proportion of tannery workers with UPCR levels exceeding 200 mg/g creatinine was 57% of the100 workers in this study. In addition, the proportion of tannery workers with UPCR levels exceeding 500 mg/g creatinine, which is classified as severe proteinuria (KDIGO, 2012), was 26% in this study. The proportion of subjects with KIM-1 levels exceeding 0.27 μg/g creatinine, a normal limit defined by a previous study (Seo et al., 2013), was 17% in this study.

3.3. Correlations of urinary levels of Cr with renal damage biomarkers

The correlation between urinary Cr level and UPCR (cut-off value of

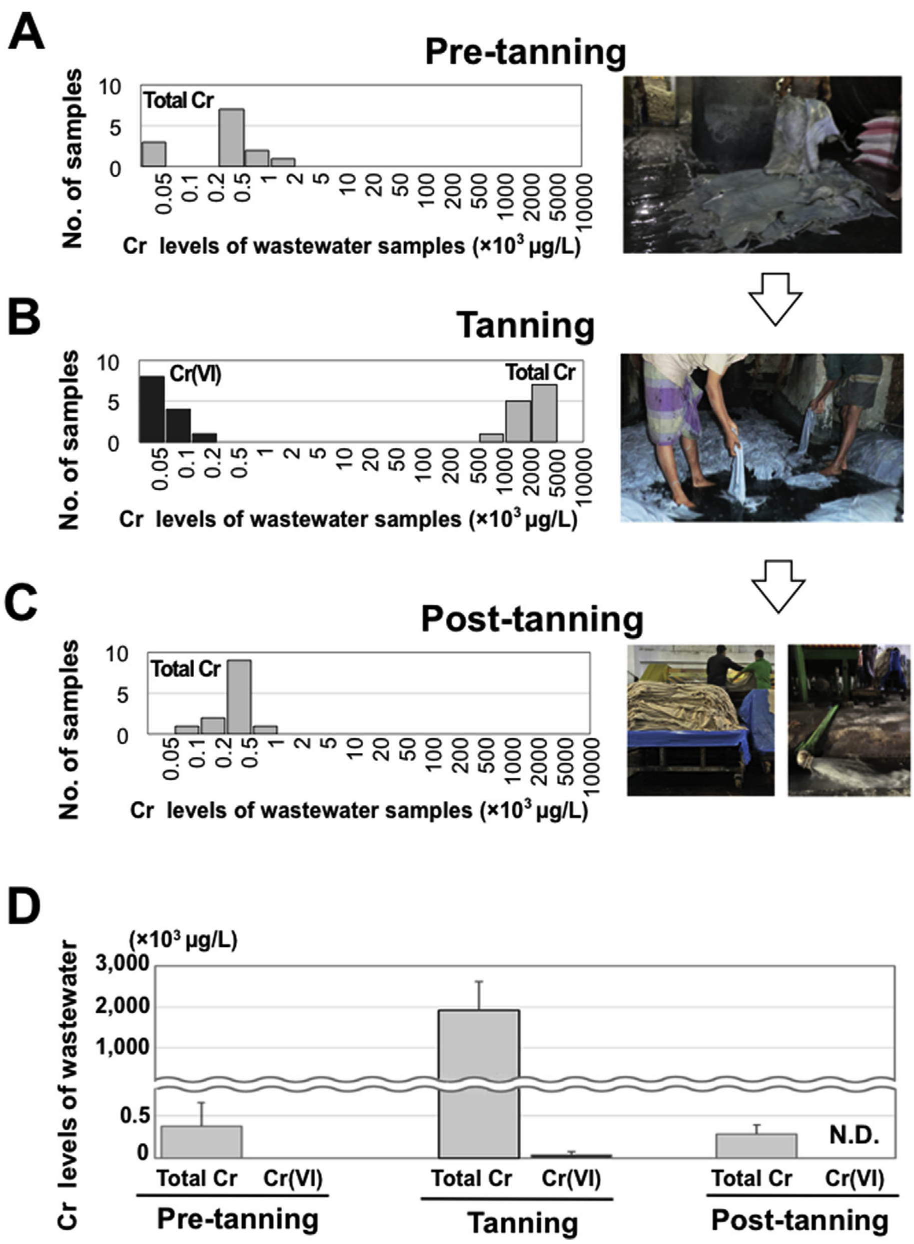

Fig. 1. Processes of leather manufacture including Cr tanning in Bangladesh. (A–C) Photographs and distributions of total Cr (gray bars) and Cr(VI) (black bars) levels in wastewater samples from processes of pre-tanning (A), tanning (B) and post-tanning (C) in tanneries are presented. (D) Concentrations (means ± SD) of total Cr and Cr(VI) in wastewater samples (n = 13) from each of the processes are presented. N.D.: not determined.

Table 1
Basic characteristics of the participants.

Characteristics	Mean ± SD (n = 100)
Age	36.77 ± 11.57
BMI	23.50 ± 3.62
Duration of tannery work (years)	14.47 ± 10.51
Cr level in urine (μg/g creatinine)	2.89 ± 4.23 *
UPCR (mg/g creatinine)	359.63 ± 326.91
KIM-1 level (μg/g creatinine)	0.138 ± 0.177

Average (geometric mean) of urinary Cr levels (2.89 μg/g creatinine) in 100 tannery workers in this study is much higher than the levels (0.10–0.12 μg/g creatinine) in general populations previously reported (Anderson et al., 1982; Heitland and Köster, 2006). BMI, body mass index; UPCR, urine total protein-to-creatinine ratio; KIM-1, kidney injury molecule-1. *geometric mean

Table 2
Correlation between urinary level of Cr and UPCR.

	OR (95%CI)	p-Value
Univariate model		
Cr in urine (μg/g Creatinine)		
< 2.89	Reference	Reference
≥ 2.89	3.7** (1.4–9.6)	0.007
Multivariate model		
Cr in urine (μg/g Creatinine)		
< 2.89	Reference	Reference
≥ 2.89	3.8** (1.4–10.3)	0.009

Odds ratios (95% CI) for UPCR in male tannery workers (n = 100) are presented. A cut-off value of 500 mg/g creatinine was used for UPCR following a previous study (KDIGO, 2012). Age, BMI and smoking status were used as cofounding factors in the multivariate model. *P*-value (***P* < 0.01) was determined by binary logistic regression analysis. OR = odds ratio, CI = confidence interval.

Table 3
Correlation between urinary levels of Cr and KIM-1.

	OR (95%CI)	p-Value
Univariate model		
Cr in urine (μg/g Creatinine)		
< 2.89	Reference	Reference
≥2.89	3.5* (1.1–10.7)	0.032
Multivariate model		
Cr in urine (μg/g Creatinine)		
< 2.89	Reference	Reference
≥2.89	5.1* (1.5–18.1)	0.011

Odds ratios (95% CI) for urinary KIM-1 level in male tannery workers (n = 100) are presented. A cut-off value of 0.27 μg/g creatinine was used for KIM-1 following a previous study (Seo et al., 2013). Age, BMI and smoking status were used as cofounding factors in the multivariate model. *P*-value (*$P < 0.05$) was determined by binary logistic regression analysis. OR = odds ratio, CI = confidence interval.

500 mg/g creatinine) is shown in Table 2. Significant correlations between urinary Cr level and UPCR level were obtained by both the univariate and multivariate models. Significant correlations remained in further multivariate analyses using different cut-off values (200, 400 and 600 mg/g creatinine) of UPCR (Supplemental Table 1).

The correlation between urinary Cr level and KIM-1 (cut-off value of 0.27 μg/g creatinine) is shown in Table 3. Significant correlations between urinary Cr level and KIM-1 level were obtained by both univariate and multivariate models. Significant correlations remained in further multivariate analyses using different cut-off values (0.10, 0.20 and 0.30 μg/g creatinine) of KIM-1 (Supplemental Table 2).

3.4. Relative contributions of urinary Cr levels to renal damage

To investigate the relative contributions of urinary Cr level and other confounders to the levels of renal damage biomarkers (UPCR and KIM-1), Nagelkerke Pseudo R^2 values were determined as described previously (Li et al., 2018). Nagelkerke Pseudo R^2 values could show the extent to which each independent variable accounted for the variation of the dependent variable in multivariate analysis. As shown in Table 4, the relative contributions of urinary Cr level to levels of UPCR and KIM-1 were higher than those of any other confounders.

Table 4
Levels of renal damage biomarkers on Nagelkerke pseudo R^2 for each item.

	Relative contribution [Pseudo R^2 (%)]	
	UPCR	KIM-1
Age	21.85	25.97*
BMI	11.15	3.52
Smoking	3.89	27.72*
Urinary Cr level (μg/g Creatinine)	61.94**	42.15**
Model redundancy	1.16	0.64

Relative contribution of each item was computed according to the following methods: Relative contribution [Pseudo R^2 (%)] = (Pseudo R^2 of the final four-variable model minus Pseudo R^2 of the nested three-variable model without the variable of interest) per (Pseudo R^2 of the final four-variable model). Model redundancy was computed according to the following method: Model redundancy [Pseudo R^2 (%)] = 100 minus total of the relative contribution [Pseudo R^2 (%)] of all four variables used in multivariate analysis. Calculation of *P*-values was performed by the likelihood ratio test for each item. Cut-off values of 500 mg/g creatinine and 0.27 μg/g creatinine were used for UPCR and KIM-1, respectively, following previous studies (KDIGO, 2012; Seo et al., 2013). *$P < 0.05$, **$P < 0.01$.

4. Discussion

Our environmental monitoring showed Cr levels in 13 wastewater samples in pre-tanning, tanning and post-tanning processes. The average concentration of total Cr in wastewater samples from the tanning process was > 5000-fold higher than those in wastewater samples from pre-tanning and post-tanning processes. Most (> 99.99%) of the Cr in wastewater from the tanning process in the tanneries was Cr(III). Furthermore, the average Cr(VI) concentration in the wastewater samples in this study was less than the health-based standard value for Cr(VI) in drinking water (50 μg/L) in Japan and Australia (NHMRC, 2011; Kato et al., 2016), suggesting a limited influence of Cr(VI) at the inside tanneries on human health.

Our epidemiological study showed that the average urinary Cr concentration in tannery workers was > 24-fold higher than those in a general population previously reported (Anderson et al., 1982; Heitland and Köster, 2006). Cr(III) but not Cr(VI) has been detected in human urinary samples regardless of exposure to either Cr(III) or Cr(VI) in previous studies (Minoia and Cavalleri et al., 1988; Corbett and Paustenbach et al., 1997). Previous studies suggested that biological reducers such as ascorbic acid, cysteine and glutathione promoted the process of metabolization from Cr(VI) to Cr(III) (Nickens et al., 2010). Therefore, the health risk of Cr(III) and Cr(VI) in humans has usually been evaluated by the chemical species of Cr in the exposure source (Ma et al., 2007; Junaid et al., 2016). Previous studies indicated that tannery workers are exclusively exposed to Cr(III) (Aitio et al., 1984; Randall and Gibson et al., 1987). Together with our environmental monitoring results, these results suggest that tannery workers suffered from excess exposure to Cr(III) inside the tanneries.

Urinary Cr level could be a good indicator for exposure to Cr in tannery workers (Aitio et al., 1984). Our analysis of the baseline characteristics of the tannery workers showed not only a > 24-fold increase of urinary Cr level but also increased levels of UPCR and KIM-1. Our logistic regression analysis further showed significant correlations of urinary Cr level with UPCR and KIM-1 levels. Our analysis of Nagelkerke Pseudo R^2 values also showed that urinary Cr level was a strong contributor to levels of renal damage biomarkers. Taken together, the results of our epidemiological study for tannery workers suggest that occupational exposure to Cr(III) could be a risk for renal damage in humans. Furthermore, a previous *in vitro* study showed Cr (III)-mediated cytotoxic effects on human cells (Shrivastava et al., 2005). A previous *in vivo* study showed selective accumulation of Cr(III) in the kidneys of rabbits (Mathur et al., 1977). Acute tubular necrosis in the kidney caused by excess exposure to Cr(III) in dietary supplements was shown as a human case report (Wani et al., 2006). Increased levels of UPCR and KIM-1 in urinary samples (Han et al., 2002; D'amico et al., 2003) in this epidemiological study suggest tubular damage of the kidneys in humans. These results suggest that accumulated Cr(III) in the kidney causes tubular damage of the kidney. Further analysis is needed in the future to clarify the mechanisms of Cr(III)-mediated renal damage.

This is an environmental issue based on the global unfair trade for leather products between developing countries and developed countries. Developing countries should consider countermeasures for health risks of workers involved in the Cr tanning process. Our original remediation system for Cr(III) and Cr(VI) with high performance (Yoshinaga et al., 2018) could be a strong tool to assuage the issue in developing countries. Developed countries should make efforts to import leather products for which reagents other than Cr have been used for the tanning process.

This study has some limitations. Despite the fact that little or no Cr (VI) was detected in fresh tannery sludge, Cr(VI) was detected in sludge at a tannery waste dumping site, indicating conversion from Cr(III) to Cr(VI) with time in the natural environment (Apte et al., 2005, 2006). Therefore, this study could not rule out the possibility that exposure to Cr(VI) outside the tanneries affects renal function of tannery workers.

More reliable results could be provided by a study with larger number of tannery workers including women at various tannery built-up areas in the world. Bangladeshi tannery workers rotated among the leather tanning processes of pre-tanning, tanning and post-tanning in a same day. It was difficult to obtain information on their working histories for each process. Therefore, further analyses were impossible in this study. Pooled urine samples for 24 h are more useful for assessing renal damage by urine samples. Levels of serum creatinine and eGFR are useful for more accurate evaluation of renal damage following clinical guidelines (KDIGO, 2012).

5. Conclusion

Chemicals including Cr(III) are generally used in tanneries in Bangladesh. Our environmental monitoring showed that > 99.99% of total Cr in wastewater samples from tanneries was Cr(III), indicating that tannery workers were exposed to Cr(III). Our epidemiological study newly demonstrated associations between urinary level of total Cr and urinary levels of renal damage biomarkers in 100 male tannery workers, indicating renal damage by excess exposure to Cr(III) in humans. There has been a case report on renal damage caused by excess intake of Cr(III) (Wani et al., 2006). Renal damage caused by excess exposure to Cr(III) has also been reported in animal studies (Mathur et al., 1977; Tandon et al., 1978). Taken together, the results suggest that there is a risk of renal damage by excess exposure to Cr(III) in humans. It may be necessary to reconsider the risk of Cr(III) exposure for human health.

CRediT authorship contribution statement

Tomoyuki Tsuchiyama: Formal analysis, Investigation, Writing - original draft. **Akira Tazaki:** Conceptualization, Writing - original draft, Supervision, Funding acquisition. **MM Aeorangajeb Al Hossain:** Formal analysis, Investigation, Resources. **Ichiro Yajima:** Conceptualization, Investigation, Supervision, Funding acquisition. **Nazmul Ahsan:** Resources. **Anwarul Azim Akhand:** Resources. **Kazunori Hashimoto:** Investigation. **Nobutaka Ohgami:** Investigation. **Masashi Kato:** Conceptualization, Writing - review & editing, Visualization, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2020.109770.

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