STATE OF MICHIGAN
DEPARTMENT OF
ENVIRONMENT, GREAT LAKES, AND ENERGY

GRETCHEN WHITMER
GOVERNOR

LIESL EICHLER CLARK
DIRECTOR

AIR QUALITY DIVISION
Constitution Hall ● 525 West Allegan Street ● P.O. Box 30260 ●
Lansing, Michigan 48909-7760
www.michigan.gov/air

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Response to Public Comments for 6:2 Fluorotelomer Sulfonic Acid (CAS No. 27619-97-2)

Summary:
Based on public comments, the Michigan Department of Environment, Great Lakes, and Energy (EGLE), Air Quality Division (AQD) has reviewed the basis for the Initial Threshold Screening Level (ITSL) for 6:2 fluorotelomer sulfonic acid (6:2 FTS). As a result of this review, the AQD has determined that the current ITSL of 1 µg/m³ (annual averaging time) is appropriate and defensible and the current screening level will be retained.

Background:

Pursuant to the Air Pollution Control Rule[1] 230(2), the AQD solicited comments on the derivation of the ITSL for 6:2 FTS from October 15, 2020 through November 17, 2020.

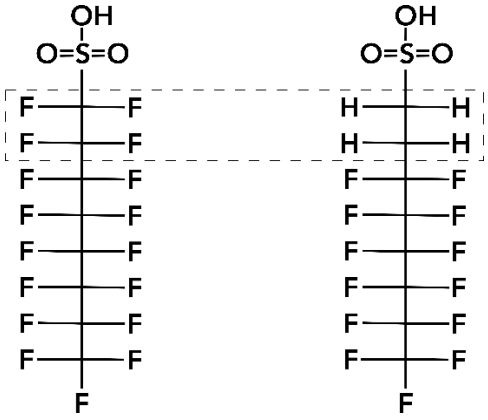
Comments and Responses:

Comment:
It is inappropriate for EGLE to apply perfluorooctane sulfonic acid (PFOS) data to support the ITSL for 6:2 FTS. 6:2 FTS should not be assumed to have similar characteristics as long-chain perfluoroalkyls. 6:2 FTS is not fully fluorinated and demonstrates differences in metabolism, elimination, and toxicological effects compared to fully fluorinated compounds.

Response:
PFOS was not used as an analog to or substitute for 6:2 FTS in these evaluations and no toxicity data from other poly- or perfluoralkyl substances (PFAS) were directly used to derive the ITSL for 6:2 FTS. Only toxicity information specifically on 6:2 FTS itself was used to derive the ITSL. Two long-term animal oral (gavage) toxicity studies reported biological effects of 6:2 FTS exposure: Sheng *et al.* (2017) and ECHA (2020). The ITSL was derived from a no-observed-adverse-effect-level (NOAEL) identified by ECHA (2020). Still, it is appropriate to compare 6:2 FTS to PFOS because Sheng *et al.* (2017) compared the two chemicals, both chemicals have a sulfonic acid functional group and at least a chain of six fully fluorinated carbons (see Figure 1).

[1] Air Pollution Control Rules in Michigan Administrative Code promulgated pursuant to Article II Pollution Control, Part 55 (Sections 324.5501-324.5542), Air Pollution Control, of the Natural Resources and Environmental Protection Act, 1994.PA 451, as amended (NREPA).

Figure 1. Comparison of PFOS and 6:2 FTS



Note: The dotted-line box represents the regions of the molecules where there are either fluorines (F) or hydrogens (H) attached to the 8-carbon backbone.

Sheng *et al*. (2017) compared bioaccumulation similarities of PFOS and 6:2 FTS in the serum and liver of mice exposed orally (via gavage) for 28-day (see Table 1).

Table 1. Bioaccumulation Data Reported by Sheng *et al.* (2017)

	Serum (µg/ml)	Liver (µg/g)
6:2 FTS	18.5	194.4
PFOS	125.4	145.9

The U.S. Environmental Protection Agency has a database called Computational Toxicology or CompTox Chemistry Dashboard that reports physical and chemical properties of chemicals (EPA, 2021). To discern the similarity or differences between 6:2 FTS and PFOS this database was queried and the properties of these two PFAS were compared (see Table 2 and 3).

Table 2. Predicted Chemical and Physical Properties of PFOS and 6:2 FTS (EPA, 2021)

Property	PFOS	6:2 FTS	Unit
LogKow: Octanol-Water	5.77	3.39	-
Melting Point	84.1	69.2	°C
Boiling Point	231	238	°C
Water Solubility	0.567	0.669	mol/L
Density	1.84	1.68	g/cm^3
Surface Tension	19.6	22.4	dyn/cm
Polarizability	20.4	20.2	$Å^3$
Molar Volume	272	250	cm^3
LogKoa: Octanol-Air	4.75	5.71	-
Henry's Law	1.80E-11	1.83E-10	$atm\text{-}m^3/mole$
Vapor Pressure	2.48E-06	8.24E-07	mmHg

Table 3. Predicted Environmental Fate and Transport Properties of PFOS and 6:2 FTS (EPA, 2021)

Property	PFOS	6:2 FTS	Unit
Bioconcentration Factor	662	188	-
Biodeg. Half-Life	4.92	4.95	days
Atmos. Hydroxylation Rate	2.01E-15	1.71E-14	cm^3/molecule*sec
Fish Biotrans. Half-Life (Km)	2.66	1.36	days
Soil Adsorp. Coeff. (Koc)	1460	947	L/kg

Comment:
6:2 FTS has "moderate hepatotoxicity" with small areas of necrosis, whereas (at the same dose) PFOS resulted in a 179% liver weight increase in mice, with marked changes in all liver enzymes and significant hepatotoxicity and necrosis.

Response:
The commenter incorrectly quoted Sheng *et al.* (2017) as saying PFOS increased liver weight by 179%. The correct increase in liver weight due to exposure to 5 mg/kg/day of PFOS exposure for 28 days should be 145%. Sheng *et al.,* 2017 states:

> In our previous studies, after 5 mg/kg/day of PFOA or PFOS exposure for 28 days, the relative liver weights of mice increased by 179% (Yan *et al.*, 2014) and 145% (unpublished), respectively. The increased relative liver weight induced by 6:2 FTSA[2] exposure (22%) showed only moderate hepatotoxicity in comparison.

Sheng *et al.* (2017) reported that dosing mice (gavage) with 5 mg/kg/day 6:2 FTS for 28 days resulted in a relative[3] liver weight (%) increase of 122%[4]. A comparison of relative liver weight increases for PFOS and 6:2 FTS is shown in Table 4.

Table 4. Comparison of Relative Liver Weight Increase (Sheng et al., 2017)

Chemical	Relative Liver Weight Increase
6:2 FTS	122%
PFOS	145%

The 122% liver weight increase of 6:2 FTS is lower than the liver weight increase observed after PFOS exposure (145%) under similar conditions (5 mg/kg/day for 28-day oral dose). Based on these results it appears that 6:2 FTS is not as hepatotoxic as PFOS. However, the two PFAS were tested at different times. It is preferable that the two PFAS be tested at the same time under the same conditions to get a more accurate assessment of the similarities or differences in liver toxicity between these two substances.

[2] 6:2 Fluorotelomer Sulfonic Acid or referred to in this document as 6:2 FTS
[3] Relative to body weight
[4] % increase = [(dose relative (%) liver wt.) - (control relative (%) liver wt.)]/(control relative (%) liver wt.)
% increase = 4.91-4.01/4.01 x 100% = 122%. Data from Sheng *et al.* (2017).

Comment:
OECD Guideline 422 rat study with a reproductive and developmental toxicity screening test component showed that 6:2 FTS is not likely a reproductive or developmental toxicant. This is also in contrast to available data on PFOS for which developmental endpoints are often the driver for risk assessments and agencies' toxicity values.

Response:
The OECD Guideline 422 for reproductive and developmental evaluations is used for screening purposes and is limited in establishing effects levels for sensitive endpoints. OECD Guideline 422 does not examine skeletal malformations in pups, visceral malformations in pups, or neurobehavioral effects in pups, and there is a limited sample size (2 pups per litter) per protocol for examination of thyroid T4 serum levels. Furthermore, the reproductive and developmental study (ECHA, 2020) was performed in one rodent species (rat). PFOS has upward of fifty mammalian reproductive and developmental toxicological studies[5], whereas 6:2 FTS has one (a possible second study in mother and new-born cord blood can also be counted; Yang *et al.,* 2016). Reproductive and developmental outcomes remain a data gap in the 6:2 FTS toxicological database.

Comment:
The Statement, "6:2 FTS is very likely to accumulate in the blood," is unfounded and not supported by the available data. There is evidence that polyfluorinated compounds, in general, are quickly eliminated. Very few human biomonitoring studies included 6:2 FTS, and it is infrequently detected. EGLE's claim that "6:2 FTS is very likely to accumulate in the blood" appears to be unfounded and contrary to available scientific data.

Response:
6:2 FTS is absorbed into the blood after oral dosing. According to Sheng *et al.* (2017), "6:2 FTSA was detected at high and very high levels in serum and liver, respectively, demonstrating bioaccumulation potential and slow elimination." The U.S. Agency for Toxic Substances and Disease Registry (ATSDR, 2018) stated that, "Perfluoroalkyls are absorbed following oral, inhalation, and dermal exposure." Environmental exposure to 6:2 FTS resulted in mother's blood and newborn cord serum (Yang *et al.,* 2016). Cord blood samples were collected immediately after delivery, while maternal blood samples were collected within the first week after delivery (Yang *et al.,* 2016). Yang et al. (2016) stated, "6:2 FTS had the highest levels and was detected in similar number of samples in both maternal and cord serum."

Comment:
It is not clear why the Air Quality Division relied upon literature that has not been peer-reviewed for decision making. The study upon which EGLE relies for the 6:2 FTS ITSL is not publicly available and was not reviewed by EGLE staff.

[5] PubMed web query using this term: reproductive developmental toxicity pfos 1763-23-1 NOT aquatic NOT fish NOT zebrafish NOT caenorhabditis elegans NOT frogs NOT chicken NOT marine NOT vacuum

Response:
The EGLE Air Quality Division (AQD) is not prohibited from using non-peer-reviewed literature either by statute or rule. Nonetheless, AQD scrutinizes these types of publications to confirm that the study has a description of the protocol that includes: a standardized methodology and experimental procedure and reports the results in sufficient details as to give evidence of the clarity and plausibility of the findings. The AQD preferably uses toxicity data found in an independent peer reviewed publication. Internal review of the ECHA findings was performed and AQD, "deemed these summaries are adequate to assess potential health risks from exposure to 6:2 FTS (EGLE, 2020). The European Chemical Agency (ECHA, 2020) also scientifically reviewed this study. Additionally, this study is compliant with Good Laboratory Practice (GLP) and according to OECD Guideline 422 (International Standard for Conducting Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Tests)(OECD, 2021). These further add to the quality of the study as it was performed to strict, standardized experimental procedure.

In February 2019, repeated attempts by EGLE to obtain the results of the original toxicological studies were made to Chemours Netherlands B.V., the listed registrant for 6:2 FTS on ECHA's registration dossier website (ECHA, 2021). Chemours did not provide the data.

If the details of the toxicity studies reported by ECHA (2020) become available, EGLE would review them and revise the ITSL if necessary.

Comment:
A slightly lower relative mean heart weight noted with statistical significance is highly questionable and may be due to random chance. No clear connection to actual impairment or adversity. No effects on absolute mean heart weight. EGLE staff could not evaluate the raw data from this study.

Response:
The lower relative mean heart weight was a statistically significant effect for the mid- and high-dose group, but not the low-dose group. Twelve animals per dose group provides enough of a sample size to discount the possibility that random variation could account for the statistically significant differences between the control and mid- and high-dose groups. The question is whether lower relative mean heart weight represents a biologically significant effect. The details (e.g., average body weight and heart weights for each dose group) are not available to discern a quantitative dose-response effect. The summary provided by Chemours to ECHA only reported that the mid- and high-dose females demonstrated the effect. Histopathology results were not reported; therefore, it is difficult to evaluate the biological significance of this effect. The conservative approach is then to identify decreased relative heart rate as a biologically significant treatment-related effect.

A small heart relative to body weight is a toxicological endpoint that is on a continuum of effects that the AQD considers adverse. To assume lower relative mean heart weight as biologically relevant is a public health protective approach. For example, if EGLE toxicologists are questioned at a public hearing by community members, it would be

difficult to explain that a statistically significant lower heart weight compared to the weight of the individual is not an adverse effect. If data (e.g., histopathology, dose group average body and heart weights) become available, EGLE would consider re-evaluating the biological significance of this endpoint.

Comment:
Route-to-route extrapolation to derive an inhalation Reference Concentration (RfC) is no longer standard best practices for risk assessment. EGLE did not consider the pharmacokinetic differences between exposure routes, first pass effects, and different results from different exposure patterns.

Response:
If there is no evidence of a first pass effect or portal-of-entry effects in the respiratory tract, AQD is permitted to use default route-to-route extrapolation as allowed by Michigan's Air Pollution Control Rule 232(b)[6]. EGLE reviewed EPA guidance documents (EPA, 2020; EPA, 2012) on the derivation of RfCs and could find no information that prohibits the use of default route-to-route such as used convert the 6:2 FTS RfD to an RfC.

Comment:
The state of the science for PFAS air analytical methods is highly uncertain making the implementation of the 6:2 FTS ITSL problematic. There is no multi-laboratory validated, published sampling methods for detecting PFAS in ambient air or in stack emissions.

Response:
A validated and published sampling method, sometimes called a "stack test," is not required to estimate the mass per time (e.g., pounds per year) air emissions of toxic air contaminants. A typical air permit will have a permit condition to record usage rate for a particular industrial process, which is then used to calculate air emission rates.

Comment:
Biomonitoring data suggest that 6:2 FTS does not accumulate in blood and should not be considered to behave similarly to perfluorooctane sulfonic acid (PFOS).

Response:
Environmental exposure to 6:2 FTS resulted in quantifiable concentrations mother's blood and newborn cord serum (Yang et al., 2016). Cord blood samples were collected immediately after delivery, while maternal blood samples were collected within the first week after delivery. Of the PFAS studied, the authors stated, "6:2 FTS had the highest levels and was detected in similar number of samples in both maternal and cord serum."

6:2 FTS was detected in both household wastewater from industrialized areas, and in biological samples (Hanssen *et al.,* 2019). In white-tailed eagle the 6:2 FTS liver concentrations ranged from 5.2-25.1 ng/g. In otter 6:2 FTS liver concentrations ranged

[6] See Footnote 1.

from 11.2-27.8 ng/g, whereas in one fox liver sample the concentration was 1.5 ng/g (Hanssen *et al.,* 2019).

Comment:
The limited toxicity data available also suggest that 6:2 FTS exhibits significantly less toxicity in laboratory animal studies than PFOS.

Response:
EGLE agrees that there is limited toxicity data on 6:2 FTS and that data indicates 6:2 FTS has less toxicity in laboratory animals than PFOS. The estimated lower toxicity is reflected in the ITSLs: the ITSL for PFOS is 0.07 µg/m³, whereas the ITSL for 6:2 FTS is 1 µg/m³. Additionally, the averaging time for PFOS ITSL is 24-hrs and the averaging time for 6:2 FTS is annual. The annual averaging time for 6:2 FTS results in lower ambient air impacts when measured using EPA's air dispersion model, i.e., AERMOD. For example, if two compounds have the same numerical value for an ITSL, one with annual and the other with a 24-hour averaging, all other things being equal, the ITSL with the longer averaging time typically is allowed a higher mass emission rate than the same ITSL value with the shorter averaging time. So not only does PFOS have a lower ITSL indicating higher toxicity, but it also has a shorter averaging time such that a lower mass emission rate is necessary to comply with the ITSL.

Comment:
Defer development of an ITSL until additional information is available for the substance.

Response:
For industrial sources subject to the Michigan's Air Toxics Rules the emissions of a toxic air contaminant must result in ambient impacts less than the screening level. If there is no published screening level, AQD typically derives one. If toxicity data are inadequate to derive an ITSL, the AQD typically establishes an ITSL based on Rule 232(1)(i) at 0.1 µg/m³ with annual averaging time. The ITSL value of 0.1 µg/m³ with annual averaging time based on Rule 232(1)(i) is commonly referred to as the default ITSL and is used when no chemical specific data are available. AQD policy is to derive ITSLs based on the best scientifically appropriate data, rather than use the default ITSL. In the case of 6:2 FTS, AQD determined that there is sufficient chemical specific toxicity information available to justify the derivation of the ITSL of 1 µg/m³ with annual averaging time. Should additional data become available, the ITSL for the 6:2 FTS ITSL can be reassessed.

Comment:
6:2 FTS is less stable in the environment, and has differences in metabolism, elimination, and toxicology compared to PFOS. While limited, serum data suggest that the substance does not accumulate in humans. Half-life for urinary excretion in rats is shorter than that for PFOS.

Response:
While not typically relevant to deriving an ITSL, sometimes environmental stability is noted when determining whether indirect pathways of exposure are important to protect public health. For example, if a chemical is persistent or bioaccumulative AQD can consider the possibility that the chemical is deposited to the earth via air deposition and assess the likelihood that the chemical can impact concentrations in water and food, including fish that live in the water. From information published by Sheng *et al.,* (2017) AQD is aware that 6:2 FTS can accumulate in the serum and liver of mice. Sheng *et al.,* (2017) stated, "6:2 FTSA was detected at high and very high levels in serum and liver, respectively, demonstrating bioaccumulation potential and slow elimination."

There is information available that supports the conclusion that 6:2 FTS does accumulate in humans. Environmental exposure to 6:2 FTS resulted in quantifiable concentrations in mother's blood and newborn cord serum (Yang *et al.,* 2016). Cord blood samples were collected immediately after delivery, while maternal blood samples were collected within the first week after delivery. Of the PFAS studied, the authors stated, "6:2 FTS had the highest levels and was detected in similar number of samples in both maternal and cord serum."

6:2 FTS may be environmentally persistent. 6:2 FTS was detected in both household wastewater from industrialized areas, and in biological samples (Hanssen *et al.,* 2019). In white-tailed eagle the 6:2 FTS liver concentrations ranged from 5.2-25.1 ng/g. In otter 6:2 FTS liver concentrations ranged from 11.2-27.8 ng/g, whereas in one fox liver sample the concentration was 1.5 ng/g (Hanssen *et al.,* 2019).

For 6:2 FTS, the rat urinary half-life (ECHA, 2020) was reported at 20.9 and 23.75 hours, using different analytical techniques. For PFOS, the rat urinary half-life was reported as 179–1,968 hours (ATSDR, 2018). EGLE agrees with the commenter that the half-life for 6:2 FTS is shorter than PFOS; however, PFOS information was not used to derive the ITSL for 6:2 FTS.

Comment:
The 3000-fold uncertainty factor is not supported scientifically and amounts to no more than a guess about the appropriate screening level. EPA has expressed concern about the use of such an excessive uncertainty factor.

Response:
Standard uncertainty factors (UFs) were used to derive the screening level for interspecies, intraspecies and duration (subchronic-to-chronic) extrapolation using EPA methodology (EPA, 1994). AQD determined that the reproductive, developmental neurobehavioral and immune toxicity of 6:2 FTS have been insufficiently characterized. Therefore, due to these knowledge gaps, a database deficiency uncertainty factor of 10 is appropriate to derive the screening level.

Comment:
The route-to-route conversion of an oral reference dose to an inhalation reference is not recommended by the US Environmental Protection Agency (USEPA[7]).

Response:
EGLE reviewed the EPA reference cited by the commenter and could find no support for this statement. Furthermore, route-to-route conversion of oral to inhalation endpoints is allowed in Rule 232(1)(b), as follows:

$$ITSL = RfD \times 70kg/20m^3$$

6:2 FTS is not expected to display toxicity to the respiratory tract or liver metabolism described as a "first pass effect." The mode of action of cardiac toxicity is not known; however, because 6:2 FTS has significant systemic effects, the route-to-route extrapolation was deemed appropriate. Should suitable data become available, the ITSL for 6:2 FTS may be reassessed.

Comment:
The delivered dose as it arrives via the human airway may be far removed from what is delivered via gavage in the laboratory rat. Toxicokinetics should be addressed for 6:2 FTS inhalation prior to setting an ITSL.

Response:
In the absence of data indicating otherwise, AQD assumes that chemicals that are not highly reactive and show potential for inhalation absorption to be treated as if they are absorbed by the respiratory tract into the blood.

Comment:
Deferral of the development of an ITSL will allow for the development of reliable methods to detect low levels of 6:2 FTS in air. Such methods are being developed at USEPA but are not yet available. Until such validated methods exist, results from various laboratories are likely to be subject to a high degree of variability.

Response:
A validated and published sampling method, sometimes called a "stack test," is not required to estimate the mass per time (e.g., pounds per year) air emissions of toxic air contaminants. A typical air permit will have a permit condition to record usage rate, which is then used to calculate air emission rates.

Comment:
The proposed 6:2 FTS ITSL of 1 µg/m³ (or 0.001 mg/m³) is three orders of magnitude more stringent than the recommended air screening level within the ECHA dossier.

[7] USEPA. ORD Staff Handbook for Developing IRIS Assessments, Version 1.0. EPA/600/R-20/137. Office of Research and Development. Washington DC (Public Comment Draft, November 2020). https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=350086

Response:
The Derived-No-Effect-Level (DNEL) for protection of workers from inhalation exposure to 6:2 FTS is reported as 1.08 mg/m³ or 1080 µg/m³ (ECHA, 2021) and is 1000 times (three orders of magnitude) more stringent than the ITSL of 1 µg/m³ (annual averaging time). AQD is generally aware of how DNELs are derived; however, the study and the effect level used to derive the value could not be identified. There is an important distinction between the ITSL and the DNEL. The ITSL is derived to be health protective for sensitive subpopulations, such as children, the elderly or those with diseases that might make individuals more susceptible to potential toxic effects from exposure to chemicals in the air. The DNEL of 1.08 mg/m³ is designed to be protective for workers who are generally healthier than the general population as a whole and even more so for sensitive individuals. AQD sometimes uses occupational exposure limits (OELs) to derive ITSLs when the underlying basis for the OEL is available for review. In fact, Air Toxics Rule 232(1)(c) has an ITSL equation, such that:

ITSL = OEL/100

Where the OEL is the American Conference of Governmental and Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) or the National Institute of Occupational Safety and Health (NIOSH) Recommended Exposure Limit (REL). OELs other than the ACGIH TLV or NIOSH REL are sometimes used to derive an ITSL when the underlying data (e.g., study and effect level) are documented and available for review. Both ACGIH and NIOSH publish documentation supporting the establishment of their OELs. If data become available to determine the basis of the 6:2 FTS DNEL, a DNEL-based ITSL could be derived as follows:

ITSL = DNEL/100 × unit conversion

Where the DNEL is 1.08 mg/m³, the ITSL would then be:

ITSL = (1.08 mg/m³)/100 × 1000 µg/mg
ITSL = 10.8 µg/m³, or 10 µg/m³ (rounded to 1 significant figure).

The averaging time applied to OEL-derived ITSLs is 8-hours.

<u>Summary and Conclusions</u>:
The poor toxicological database available to evaluate the toxicity of 6:2 FTS via the inhalation pathway results in a ITSL that is likely to change once more data become available. Commenters were rightly concerned about the reliability of the ECHA summary and the uses of relative cardiac weight as a valid effect level. EGLE determined that the cardiac effects are likely due to exposure to 6:2 FTS, present a legitimate public health concern, and are appropriate to use to derive an inhalation screening level. Standard EPA uncertainty factors were used to derive the ITSL and were justifiable given the poor toxicological database. The oral-to-inhalation or route-to-route extrapolation used Rule 232(1)(b) is appropriate under Michigan's Air Toxics Rules. This method of route-to-route extrapolation was deemed appropriate because no portal of entry (respiratory) effects and no first pass liver transformation of the 6:2 FTS molecule are expected.

A good portion of the comments received were about EGLE using PFOS as a surrogate for 6:2 FTS. EGLE did not use PFOS toxicity data to derive the ITSL for 6:2 FTS because the chemical specific toxicity data available for 6:2 FTS was adequate and appropriate for the derivation. Should new information become available on 6:2 FTS, EGLE can consider reassessing the ITSL.

The primary AQD reviewer for these comments was Mike Depa, Senior Toxicologic, AQD Toxics Unit. The secondary (peer) reviewers were Eric Wildfang, RRD Toxicology Unit Manager and Grace Kuan, Toxicologist, RRD Toxicology Unit.

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