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Provisional Peer Reviewed Toxicity Values for

2,4,6-Trichlorophenol

(CASRN 88-06-2)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

Acronyms and Abbreviations

bw	body weight
cc	cubic centimeters
CD	Caesarean Delivered
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act of 1980
CNS	central nervous system
cu.m	cubic meter
DWEL	Drinking Water Equivalent Level
FEL	frank-effect level
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
g	grams
GI	gastrointestinal
HEC	human equivalent concentration
Hgb	hemoglobin
i.m.	intramuscular
i.p.	intraperitoneal
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
i.v.	intravenous
kg	kilogram
L	liter
LEL	lowest-effect level
LOAEL	lowest-observed-adverse-effect level
LOAEL(ADJ)	LOAEL adjusted to continuous exposure duration
LOAEL(HEC)	LOAEL adjusted for dosimetric differences across species to a human
m	meter
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mg/kg	milligrams per kilogram
mg/L	milligrams per liter
MRL	minimal risk level
MTD	maximum tolerated dose
MTL	median threshold limit

NAAQS	National Ambient Air Quality Standards
NOAEL	no-observed-adverse-effect level
NOAEL(ADJ)	NOAEL adjusted to continuous exposure duration
NOAEL(HEC)	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration
p-RfD	provisional oral reference dose
PBPK	physiologically based pharmacokinetic
ppb	parts per billion
ppm	parts per million
PPRTV	Provisional Peer Reviewed Toxicity Value
RBC	red blood cell(s)
RCRA	Resource Conservation and Recovery Act
RDDR	Regional deposited dose ratio (for the indicated lung region)
REL	relative exposure level
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	Regional gas dose ratio (for the indicated lung region)
s.c.	subcutaneous
SCE	sister chromatid exchange
SDWA	Safe Drinking Water Act
sq.cm.	square centimeters
TSCA	Toxic Substances Control Act
UF	uncertainty factor
µg	microgram
µmol	micromoles
VOC	volatile organic compound

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PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR 2,4,6-TRICHLOROPHENOL (CASRN 88-06-2)

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (EPA's) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1. EPA's Integrated Risk Information System (IRIS).

2. Provisional Peer-Reviewed Toxicity Values (PPRTV) used in EPA's Superfund Program.

3. Other (peer-reviewed) toxicity values, including:

   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
   - California Environmental Protection Agency (CalEPA) values, and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in EPA's Integrated Risk Information System (IRIS). PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the EPA IRIS Program. All provisional toxicity values receive internal review by two EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multi-program consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a five-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV manuscripts conclude that a PPRTV cannot be derived based on inadequate data.

Disclaimers

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and RCRA program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV manuscript and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

Questions Regarding PPRTVs

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

Neither an RfD or RfC for 2,4,6-trichlorophenol (2,4,6-TCP) is available on IRIS (U.S. EPA, 2007) or in the HEAST (U.S. EPA, 1997). IRIS (U.S. EPA, 2007) provides an OSF and IUR. The Drinking Water and Health Advisories list (U.S. EPA, 2000) does not include an oral RfD for 2,4,6-TCP. ATSDR published a Toxicological Profile for 2,4,6-Trichlorophenol (ATSDR, 1990) in which an intermediate-duration oral MRL of 0.042 mg/kg-day was derived, based on a NOAEL of 4.2 mg/kg-day and a LOAEL of 42 mg/kg-day for reduced litter size in female Sprague-Dawley rats exposed to 2,4,6-trichlorophenol in the drinking water from 3 weeks of age through breeding and parturition (Exon and Koller, 1985). ATSDR subsequently published an updated Toxicological Profile for Chlorophenols (ATSDR, 1997), providing an intermediate-duration oral MRL of 0.003 mg/kg-day for chlorophenols as a class, based on decreased delayed type hypersensitivity response to bovine serum albumin in rats exposed to 2,4-dichlorophenol in drinking water (Exon and Koller, 1985). ATSDR (1997) did not provide an intermediate-duration oral MRL for 2,4,6-TCP per se. The CARA database (U.S. EPA, 1991,

1994) lists a Health Effects Assessment for 2,4,6-TCP (U.S. EPA, 1984) and a Health and Environmental Effects Document for Chlorinated Phenols (U.S. EPA, 1987), neither of which developed an RfD, because the focus was on carcinogenic potential. The NTP Status Report (NTP, 2000) and IARC (1999) were also searched for relevant information. Updated literature searches were conducted from 2000 to present (original search was from 1996). The databases searched were TOXLINE, MEDLINE, CANCERLIT, CCRIS, TSCATS, HSDB, RTECS, GENETOX, DART/ETICBACK, and EMIC/EMICBACK.

REVIEW OF THE PERTINENT LITERATURE

Human Oral Studies

No information was located concerning health effects in humans following oral exposure to 2,4,6-TCP.

Animal Oral Studies

NCI (1979) performed chronic oral studies designed to assess the carcinogenicity of 2,4,6-TCP in Fischer 344 rats and B6C3F$_1$ mice. Groups of 50 male and 50 female Fischer 344 rats were given 2,4,6-TCP (96-97% pure) in the diet at concentrations of 5000 or 10,000 ppm for 106 or 107 weeks. The authors did not estimate daily doses, nor did they report food consumption. Assuming a food factor of 0.05 for a chronic oral study in the rat (U.S. EPA, 2007), estimated doses of 2,4,6-TCP were 250 and 500 mg/kg-day for the 5000- and 10,000-ppm exposure groups, respectively. Groups of 50 male mice were similarly exposed to 5000 or 10,000 ppm for 105 weeks. Assuming a food factor of 0.15 for a chronic oral study in the mouse (U.S. EPA, 2007), the doses were estimated to be 750 and 1500 mg/kg-day, respectively. Groups of 50 female mice were given 10,000 or 20,000 ppm for 38 weeks; the concentrations were reduced to 2500 and 5000 ppm for the remaining 67 weeks of the study, due to excessively low mean body weights among treatment groups. The time-weighted average feed concentrations for the female mice were 5214 and 10,428 ppm in the low- and high-dose groups, respectively (doses of 782 and 1564 mg/kg-day assuming a food factor of 0.15 for a chronic oral study in the mouse). Groups of 20 rats and 20 mice of each sex served as controls. Animals were observed twice daily for clinical signs of toxicity, and gross and microscopic pathological examinations were performed on all major organs and tissues of animals that died or were found in a moribund state during the study (except for cases of cannibalization or autolysis) and on those surviving until terminal sacrifice. Incidences of various neoplastic and nonneoplastic lesions were reported, but none are applicable for derivation of the RfD. There were no significant dose-related trends in mortality in rats or mice of either sex. Throughout the course of the study, male and female rats and mice exhibited dose-related lower mean body weights than controls at the 38-week time period, when concentrations of 2,4,6-TCP were lowered, as well as throughout the remainder of the study. Clinical signs were common to both dosed and control groups of rats and mice. Male rats, only, exhibited dose-related significantly increased incidences of lymphomas or

leukemias. Leukocytosis, monocytosis, and bone marrow hyperplasia were noted in some treated male and female rats not having lymphoma or leukemia, but not in the 20 control rats. In mice, a significantly increased incidence of hepatocyte hyperplasia was observed for mid-dose males. Other hepatotoxic effects (inflammation, necrosis) were commonly seen in the livers of dosed mice. Hepatocellular carcinomas or adenomas occurred in mice at incidences that were dose-related. For the purpose of deriving an RfD, all noncancer effects reported for both rats and mice in NCI (1979) are considered to be related to the carcinogenic process and are not relevant for deriving an RfD.

In preliminary range-finding studies by NCI (1979), groups of rats and mice (5/sex/species) were exposed to 10,000-46,000 ppm (rats) or 6800-31,500 ppm (mice) of 2,4,6-TCP in the diet for 7 weeks. Assuming a food factor of 0.1 for a subchronic oral study in rats and a food factor of 0.15 for a subchronic oral study in mice (U.S. EPA, 2007), estimated dose ranges were 1000-4600 mg/kg-day in rats and 1020-4725 mg/kg-day in mice. Relative to controls, dose-dependent lower mean body weights were reported in all exposed groups of rats, and in groups of mice at doses $\geq$735 mg/kg-day (males) or $\geq$1075 mg/kg-day (females). Survival was 100% for rats and mice (of both sexes) consuming doses $\leq$1470 mg/kg-day and $\leq$3225 mg/kg-day, respectively. The highest dose in rats (4600 mg/kg-day) resulted in the death of 2/5 males and 3/5 females. At the highest dose in mice (4725 mg/kg-day), mortality was observed in two mice of each sex. In rats, histopathologic signs of toxicity were seen only at the highest dose (4600 mg/kg-day) and consisted of moderate to marked increased splenic hematopoiesis in males and females and midzonal vacuolation of hepatocytes in males. Histological examination gave no indication of treatment-related toxicity in male and female mice of the 1075 mg/kg-day dose groups. The authors did not indicate whether or not histopathologic effects were seen at lower doses or the highest dose (4725 mg/kg-day) in mice. No other relevant data were provided. The lowest treatment level (735 mg/kg-day) is considered to be a LOAEL, but the dose levels in this study are too high to be useful for RfD derivation.

In a subchronic gavage study (Bercz et al., 1990), groups of 10 male and 10 female Sprague-Dawley rats, 49 days of age, were administered 2,4,6-TCP in oral doses of 0, 80, 240, or 720 mg/kg-day by gavage (in corn oil) for 90 days. Clinical observations were made daily; mortality and morbidity checks were performed twice daily. Body weights were recorded weekly, at which time animals were examined for obvious signs of abnormalities. Food consumption was measured weekly, ophthalomoscopic examinations were performed prior to treatment and during the final week of the study. Extensive analyses of hematology, blood chemistry, and urine profiles were performed at sacrifice. Comprehensive gross and microscopic examinations were performed on major tissues and organs, as well as all gross lesions. There were no significant treatment-related effects regarding mortality, body weight, food consumption, ophthalmology, or hematology. Significant dose-related effects consisted of increased absolute or relative liver weight in mid- and high-dose males and females and increased absolute and relative kidney weight in high-dose males. Other significant effects occurred primarily in the high-dose group, and included clinical signs (urine staining and salivation); increased relative testes weight (males), absolute lung, and relative adrenal weight (females); increased serum

albumin, total protein, alkaline phosphatase, and ALT (males); decreased BUN (females); and decreased urinary pH (males and females). There were no significant treatment-related adverse effects in the low-dose groups of either sex. Histopathologic examination did not reveal pathological lesions that could be correlated to treatment-related changes in organ weights or biochemistry values. This study establishes a subchronic NOAEL and LOAEL of 80 and 240 mg/kg-day, respectively.

In a subchronic (1-generation female reproduction) study, groups of 12-14 female Sprague-Dawley rats were exposed to 2,4,6-TCP (98% pure) at concentrations of 0, 3, 30, or 300 ppm in the drinking water (Exon and Koller, 1985). Animals were exposed from 3 weeks of age through breeding (at 90 days of age to unexposed male rats) and parturition, for a total exposure period of approximately 13 weeks. The study authors did not report dam body weight or water consumption data, nor did they provide dose estimates. Based on the assumption that rats consume drinking water at a rate of 10% of their body weight per day (U.S. EPA, 2007), 2,4,6-TCP dose levels of 0.30, 3.0, and 30 mg/kg/day for the 3-, 30-, and 300-ppm exposure groups, respectively, were calculated. Following parturition, treatment of dams ceased and pups were observed until weaning. Reproductive toxicity was assessed with respect to percent conception, litter size, number of stillborn, birth and weaning weight, and survival to weaning. Maternal parameters such as body weight during pregnancy, feed consumption, and clinical signs of toxicity were not reported. Significantly decreased mean litter size ($p \leq 0.10$) was noted in the 300-ppm (30 mg/kg-day) group (9.1 pups/litter vs 12.1 in controls and 11.3 and 11.2 in the low- and mid-dose groups, respectively). Although the level of statistical significance (0.10) is higher than that commonly used (0.05), the magnitude of the decrease (25%) is considered to be biologically significant. Similar decreases in litter size were seen with other chlorophenols tested in this study (2-chlorophenol, 2,4-dichlorophenol), lending some support to this being an important endpoint for this class of chemicals. It is noteworthy, however, that average control litter size varied over a considerable range in the three experiments (9.8-12.1). This study identified a LOAEL of 30 mg/kg-day (300 ppm exposure group) and a NOAEL of 3.0 mg/kg-day (30 ppm exposure group) for 2,4,6-TCP, based on decreased mean litter size.

Exon and Koller (1985) also reported a continuation of the initial subchronic study, in which 3-week-old weanling Sprague-Dawley rats (10/exposure group) were randomly selected from the litters generated in the reproductive phase of the study were exposed to the same concentrations of 2,4,6-TCP in the drinking water as those previously used in the exposure of the corresponding dams. The exposure period covered an additional 12 weeks. Following exposure termination, immunologic assays were performed to assess humoral immunity, cell-mediated immunity, and macrophage function. Body weights and weights of liver, spleen, and thymus were recorded. No other information was reported regarding study design or endpoints examined. There were no statistically significant exposure-related effects on immune responses, although the authors noted that antibody levels, delayed type hypersensitivity responses, and macrophage numbers were consistently greater in 2,4,6-TCP-exposed rats, compared with controls. There were no significant exposure-related effects on mean body or thymus weights. The 300-ppm exposure group exhibited significantly increased mean spleen weight (1.07 g vs

0.93 g in controls). Significantly increased mean liver weight was observed in both 30- and 300-ppm exposure groups (12.5 and 14.1 g, respectively, vs 10.9 g in controls). Significantly increased mean spleen and liver weights were also seen in rats similarly exposed to 300-ppm of 2,4-DCP. The effects related to immune response and increased liver weight (at 30 mg-kg-day) were not considered to be adverse by Exon and Koller (1985).

Blackburn et al. (1986) administered 2,4,6-TCP (99% pure) to groups of 30 (low- and mid-dose) or 40 (controls and high-dose) adult female Long-Evans hooded rats in oral doses (gavage, in corn oil) of 0, 100, 500, or 1000 mg/kg-day, 5 days per week for 2 weeks, followed by dosing 7 days per week during mating with unexposed males of the same strain and throughout 21 days of gestation. Body weights were recorded daily from the beginning of treatment until delivery. Females that had not delivered by gestation day 24 were sacrificed, and ovaries and uteri examined for signs of post implantation loss. For those females delivering pups, date of delivery, sex ratio of the litter, and male and female pup body weights were recorded. Litters were culled to 8 pups (approximately equal numbers of males and females) on postpartum day 4. Body weights were recorded weekly thereafter and litters were culled to 2 males and 2 females each at weaning. Female pups were monitored for time of vaginal opening. On postpartum day 42, all remaining pups were sacrificed. Necropsy was limited to establishing whether or not intubation was the cause of death in treated dams that succumbed prior to the termination of treatment. Survival was 38/39, 29/29, 25/30, and 24/40 in 0-, 100-, 500-, and 1000-mg/kg-day groups of treated dams, respectively. The majority of deaths, particularly in the high-dose dams, were due to intubation errors. However, 3/16 high-dose deaths were attributed to 2,4,6-TCP exposure. Urogenital staining was noted in the high-dose group. Dose-related significantly lower mean body weights (relative to controls) were observed in dams at the end of the first and second weeks of pre-mating treatment, as well as throughout the first 14 days of gestation (the actual body weight values could not be determined from the graphically-presented body weight data). No significant treatment-related maternal body weight effects were apparent on gestation day 21. There were no statistically significant dose-related differences in breeding success, although breeding success was low in all study groups (63, 72, 60, and 50% for 0-, 100-, 500-, and 1000-mg/kg groups, respectively). No significant treatment-related differences were seen in mean litter sizes or pup survival. Mean litter body weights were significantly depressed in pups of the 500- and 1000-mg/kg groups initially, but from postpartum day 4 onward, there were no significant differences in mean litter body weights of any exposure group, relative to controls. The study authors indicated that the initial depressed pup body weights were most likely a reflection of maternal toxicity, as evidenced by increased mortality, clinical signs (urogenital staining), and decreased body weights in mid- and high-dose dams. A maternal FEL of 500 mg/kg-day is identified in this study based on decreased survival.

In a second experiment reported in Blackburn et al. (1986), male Long-Evans hooded rats (25 high-dose rats, 15 per group at other dose levels) were administered 2,4,6-TCP (99% pure) in oral doses (gavage, in corn oil) of 0, 100, 500, or 1000 mg/kg-day, 5 days per week for 11 weeks (Blackburn et al., 1986). Males used in this study had initial baseline sperm counts of 20 million or more and ejaculation latencies of 30 minutes or less. After 10 weeks of treatment, copulatory

behavior and semen profiles were evaluated. Following 11 weeks of treatment, high-dose and control males were mated with unexposed females for fertility evaluation. Once mating was confirmed, females were isolated and followed until sacrifice on gestation day 18. Numbers of resorptions and fetal sex, weight, and viability were recorded. Treated and control male rats were sacrificed one week later, and blood was drawn for testosterone analysis. Weights of liver, kidney, lung, adrenal, spleen, heart, testis, prostate, seminal vesicle, vas deferens, and epididymis were recorded. Sperm counts were performed using epididymal tissue. The only consistent clinical sign of toxicity was that of urogenital staining, observed in all 2,4,6-TCP-treated groups. There were no additional clinical signs of toxicity among rats that died during treatment, and due to autolysis, necropsy of these rats was limited to examination for potential intubation errors. Treatment-related mortality was observed in 8/25 high-dose males during the first 4 weeks of treatment. All other deaths in treated animals were attributed to intubation errors. There were no significant treatment-related differences in mean body weights at most time points during treatment. No treatment-related adverse effects were seen in evaluations of mating behavior, which included mount and ejaculation latencies, or sperm count, motility, or morphology. No significant treatment-related differences were detected in male organ weights or plasma testosterone. There were no significant treatment-related effects on litter size, sex ratio, mean pup weight by sex, number of dead fetuses, or number of resorption and implantation sites in evaluations of litters produced by 2,4,6-TCP-treated males mated to untreated females. The lowest dose level of 100 mg/kg-day is considered to be a LOAEL based on clinical observations (urogenital staining).

DERIVATION OF A PROVISIONAL RfD FOR 2,4,6-TRICHLOROPHENOL

A provisional RfD for 2,4,6-TCP can be derived from the oral reproductive toxicity study in rats conducted by Exon and Koller (1985). This study identified a NOAEL of 3.0 mg/kg-day and a LOAEL of 30 mg/kg-day, based on decreased litter size in female Sprague-Dawley rats exposed to 2,4,6-TCP in the drinking water for 10 weeks prior to mating (weanlings when started) and continuing throughout mating and gestation. In the same study, decreased litter size was also noted for similar exposure to 2-chlorophenol and 3,4-dichlorophenol, thus lending some support to this finding. However, the decrease in litter size was small and there was considerable variation in litter size among controls in the three experiments. Apparently conflicting results were reported by Blackburn et al. (1986), in a study in which no reproductive toxicity was observed in female Long-Evans rats administered 2,4,6-TCP by daily gavage in corn oil starting 2 weeks prior to mating (adults when started) and continuing throughout mating and gestation at doses that were in excess of an order of magnitude higher than those estimated for Sprague-Dawley rats used in the Exon and Koller (1985) study. The disparity in results may be attributable, at least in part, to the use of different rat strains and procedural differences [Exon and Koller (1985) initiated exposure to weanlings 10 weeks prior to mating via the drinking water, whereas Blackburn et al. (1986) started dosing of adults 2 weeks prior to mating via bolus oral gavage.] The study of Blackburn et al. (1986) was limited by low reproductive success in all groups, including controls. The marginally increased mean absolute liver weight (11% greater

than controls) reported for the 30 ppm group in the Exon and Koller (1985) continuation study is not considered to be an adverse effect. Also, the effects related to immune response reported by Exon and Koller (1985) are not considered for defining the LOAEL, as there is no dose-response relationship established.

The provisional RfD is derived by dividing the subchronic NOAEL of 3.0 mg/kg-day by an uncertainty factor of 3000 (10 for extrapolation from subchronic to chronic exposure duration, 10 for extrapolation from rodents to humans, 10 for protecting sensitive individuals, and 3 for deficiencies in the database, particularly the lack of a multigeneration reproduction study and supporting long-term toxicity studies in other species). The **provisional RfD** derived in this way **is 3.0 mg/kg-day ÷ 3000 = $1x10^{-3}$ or 1E-3 mg/kg-day.**[1]

STATEMENT OF CONFIDENCE

Confidence in the key studies is low. Although the critical animal study (Exon and Koller, 1985) examined reproductive endpoints, study details were limited, a single generation was produced, and only females were exposed. The study did, however, identify both a NOAEL and a LOAEL for reproductive effects. Confidence in the database is low due to the lack of a multigeneration reproduction study and supporting long-term toxicity studies. Consequently, there is low confidence in the provisional RfD.

DERIVATION OF A PROVISIONAL RfC FOR 2,4,6-TRICHLOROPHENOL

No values are developed due to lack of relevant information.

DERIVATION OF A PROVISIONAL CARCINOGENICITY ASSESSMENT FOR 2,4,6-TRICHLOROPHENOL

Cancer values are provided on IRIS (U.S. EPA, 2007).

[1] The RfD differs from the ATSDR intermediate-duration MRL of 4E-2 mg/kg-day. ATSDR never applies a database uncertainty factor and did not apply a derivation UF. When these UFs are applied the value would be divided by an additional 30 or 1E-3 which is identical to the RfD.

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