An IARC Evaluation of Polychlorinated Dibenzo-*p*-dioxins and Polychlorinated Dibenzofurans as Risk Factors in Human Carcinogenesis

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The International Agency for Research on Cancer (IARC) Monographs program reevaluated polychlorinated dibenzo-*p*-dioxins and evaluated polychlorinated dibenzofurans as possible carcinogenic hazards to humans in February 1997, using the most recent epidemiologic data on exposed human populations, experimental carcinogenicity bioassays in laboratory animals, and supporting evidence on relevant mechanisms of carcinogenesis. 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) was evaluated as *carcinogenic to humans* (IARC group 1 classification) on the basis of *limited* evidence of carcinogenicity to humans derived from follow-up of workers who had been heavily exposed in industrial accidents and *sufficient* evidence of carcinogenicity in experimental animals. The evaluation also considered the following supporting evidence: TCDD is a multisite carcinogen in experimental animals and has been shown by several lines of evidence to act through a mechanism involving the aryl hydrocarbon receptor; this receptor is highly conserved in an evolutionary sense and functions the same way in humans as in experimental animals; tissue concentrations of TCDD are similar in heavily exposed human populations in which an increased overall cancer risk was observed and in exposed rats that developed tumors in carcinogenicity tests. Other polychlorinated dibenzo-*p*-dioxins, the nonchlorinated dibenzo-*p*-dioxin, and polychlorinated dibenzofurans were evaluated as *not classifiable as to their carcinogenicity to humans* (group 3). — *Environ Health Perspect* 106(Suppl 2):755–760 (1998). *http://ehpnet1.niehs.nih.gov/docs/1998/Suppl-2/755-760mcgregor/abstract.html*

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The program of the International Agency for Research on Cancer (IARC) *Monographs on the Evaluation of Carcinogenic Risks to Humans* convened a Working Group of experts and observers from 11 countries in Lyon, France, 4 to 11 February 1997 to evaluate the evidence that polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) might be risk factors for human cancer (*1*). Although quantitative information, including dose–response relationships, was important in reaching the conclusions of the meeting, the question of quantitative risk estimation was not addressed by the Working Group. This meeting marked the third time PCDDs were considered within this program. In 1977 few data were available and no evaluation of PCDDs could be made, either on the basis of animal carcinogenicity evidence or reports of people exposed to contaminated herbicides (*2*). By 1987 the animal carcinogenicity data had developed to the stage where there was *sufficient evidence* for the carcinogenicity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD or dioxin, the PCDD that has caused most concern), but the epidemiologic evidence remained *inadequate* (*3*). Accordingly, at that time TCDD was evaluated as *possibly carcinogenic to humans* (IARC group 2B classification), whereas all other PCDDs were considered *not classifiable as to their carcinogenicity to humans* (group 3).

Occurrence and Exposure to PCDDs and PCDFs

PCDFs are formed as inadvertent by-products in the production and use of polychlorinated biphenyls (PCBs) and, in combination with PCDDs, in the production of chlorophenols; PCDFs have been detected as contaminants in these products (*4–6*). PCDFs and PCDDs also may be produced in thermal processes such as incineration and metal processing and in the bleaching of paper pulp with free chlorine (*7–9*). PCDFs also are found in residual waste from the production of vinyl chloride and the chloralkali process for chlorine production (*10–14*). The relative amounts of PCDF and PCDD congeners produced depend on the production or incineration process and vary widely.

PCDDs and PCDFs are ubiquitous in soil, sediment, and air. Descriptions of exposure and biologic monitoring information can be found in *Polychlorinated Dibenzo*-para-*Dioxins and Polychlorinated Dibenzofurans* (*1*). Excluding occupational or accidental exposures, most human exposure to PCDDs and PCDFs occurs as a result of eating meat, milk, eggs, fish, and related products, as both PCDDs and PCDFs are persistent in the environment and accumulate in animal fat. Occupational exposures to both PCDDs and PCDFs at higher levels have occurred since the 1940s as a result of the production and use of chlorophenols and chlorophenoxy herbicides; PCDF exposure also results from metal production and recycling. Even higher exposures to PCDDs have occurred sporadically in relation to accidents in these industries. High exposures to PCDFs have occurred as a result of accidents involving electrical equipment containing PCBs (*15*) and from the consumption of contaminated rice oils. The latter have caused specific illnesses to which the locally descriptive names for oil disease have been given: Yusho in Japan (*16*) and Yu-cheng in Taiwan (*17*).

In human tissues, current mean background levels of TCDD are in the range of 2 to 3 ng/kg fat; the sum of the penta- and

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Abbreviations used: AhR, aryl hydrocarbon receptor; HBV, hepatitus B virus; HCV, hepatitus C virus; IARC, International Agency for Research on Cancer; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzo-*p*-dioxin; PCDF, polychlorinated dibenzofuran; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.

hexachlorinated PCDF congeners commonly found in human tissues is generally in the range of 10 to 100 ng/kg fat. Tissue concentrations following accidental exposures have led to increases above these background levels of up to four orders of magnitude for TCDD and one or more orders of magnitude for PCDFs. Because of the long half-lives of many of these substances in humans (e.g., approximately 7 years for TCDD), a single acute exposure from the environment results in the exposure of potential target tissues over many years; this property also allows accurate extrapolation of concentrations in tissues back to the known dates of accidental exposure, thereby permitting estimation of individual levels of acute exposure with unusually high precision.

Evidence for the Carcinogenicity of PCDDs

Human Carcinogenicity Data

The most informative studies for causal inference are those in which it is clear that the highest exposures to the chemical in question have occurred because, if they are causal, these will produce the highest cancer risks. For this reason, attention focused on the most exposed subcohorts within cohorts with adequate latency, although other cohort studies and numerous case–control studies also played a role in the evaluation. Following these criteria, the most important studies for the evaluation of TCDD are four cohort studies of herbicide producers [one each in the United States (*18*) and the Netherlands (*19*), two in Germany (*20,21*)]. These studies involve the highest exposures to TCDD among all epidemiologic studies. The cohort of residents in a contaminated area from Seveso, Italy, is well known, but the exposures at Seveso were lower and the follow-up shorter than those in the industrial settings (*22*). Most of the four industrial cohorts include analyses of subcohorts considered to have the highest exposure and/or longest latency. Additional cohort and case–control studies of herbicide applicators (*23*), military personnel in Vietnam, as well as Operation Ranch Hand personnel (*24*), who have considerably lower exposures to TCDD, were not considered critical for the evaluation.

An increased risk for all cancers combined (approxmately 1.4-fold) was seen in the cohort studies. This magnitude of increase occurred in subcohorts considered to have the heaviest TCDD exposure within the cohorts. Furthermore, statistically significant positive dose–response trends for all cancers combined were present in the largest and most heavily exposed German cohort (*21*). A positive trend ($p = 0.05$) was also seen in the smaller German cohort where an accident occurred with release of large amounts of TCDD; the positive trend in this cohort was limited to smokers (*20*). Cumulative dose in both these trend analyses was estimated by combining data from blood and adipose tissue TCDD levels and knowledge of job categories, work processes, and dates of exposure. This information was used with elimination half-time data in kinetic models for extrapolation back to the time of accidental exposure. Increased risks for all cancers were also seen in the longer duration, longer latency subcohort of a study in the United States (*18,25*). These positive trends with increased exposure tend to reinforce the overall positive association between all cancers combined and exposure, making it less likely that the increase is explained by confounding, either by smoking or by other carcinogenic exposures in industrial settings.

An increased risk of lung cancer is also present in the most informative cohort studies, again especially in the more highly exposed subcohorts. The relative risk for lung cancer in the combined highly exposed subcohorts was estimated to be 1.4 (statistically significant). It is possible that lung cancer relative risks of this order could result from confounding by smoking, but only if there is a pronounced difference in smoking habits between the exposed population and the referent populations, a difference that seems unlikely. It therefore seems unlikely that confounding by smoking can explain all the excess lung cancer risk, although it could explain part of it. It is also possible that other occupational carcinogens, many of which would affect the lung, are causing some confounding. Several other malignant neoplasms have been reported sporadically to be at increased prevalence in some populations exposed to TCDD, but none of these were consistently increased within the individual cohorts. For example, soft-tissue sarcomas were present in the Seveso population, but only in the zone that overall had the lowest exposure (*25*); no such increase was present in the German (*20,21*) or Dutch (*19*) cohort studies.

Overall, the strongest evidence for the carcinogenicity of TCDD is for all cancers combined rather than for any specific site. There are few examples of agents that cause an increase in cancers at many sites; examples are smoking and ionizing radiation in atomic bomb survivors (for both agents, however, there are clearly elevated risks for certain specific cancer sites). This lack of precedent for a multisite carcinogen without particular sites predominating means that the epidemiologic findings must be treated with caution. On the basis of this information, it was considered that there is *limited evidence* in humans for the carcinogenicity of TCDD.

In contrast, there was *inadequate evidence* in humans for the carcinogenicity of all other PCDDs.

Animal Carcinogenicity Data

In a number of experiments with rats and mice in which TCDD was administered, increases in the incidence of liver tumors were consistently found in both males and females. In addition, several other neoplasms were increased in rats, mice, and Syrian hamsters, including thyroid follicular cell adenomas, lymphomas, and alveolar/bronchiolar adenomas and carcinomas; but these effects were dependent on the species, sex, and route of administration of TCDD. In addition, tumors developed at a number of unusual sites such as the tongue, hard palate, and nasal turbinates in rats (*26–31*). Although they are extremely low, the doses resulting in increased tumor incidence in rodents are very close to doses that are toxic in the same species. These data led to the conclusion that there is *sufficient evidence* in experimental animals for the carcinogenicity of TCDD. It is notable that the tissue concentrations of TCDD in one of the studies with rats given doses that produced a significant increase in tumor incidence were in the same range as those experienced in some highly exposed human populations.

Evaluation of much smaller databases (*32,33*) led to the conclusion that there is *limited evidence* in experimental animals for the carcinogenicity of a mixture of 1,2,3,6,7,8- and 1,2,3,7,8,9-hexaCDD and that there was *inadequate evidence* for the carcinogenicity in experimental animals of 2,7-diCDD, 1,2,3,7,8-pentaCDD, and 1,2,3,4,6,7,8-heptaCDD. The nonchlorinated dibenzo-*p*-dioxin has been thoroughly tested in rodents, with negative results (*33*).

Evidence for the Carcinogenicity of PCDFs

Human Carcinogenicity Data

Two incidents, one in Japan (Yusho) (*35,36*) and one in Taiwan (Yu-cheng) (*37*), each involving about 2000 cases, involved individuals' exposure to sufficient

doses of PCBs and PCDFs to produce symptoms. Fatal liver disease is now 2 to 3 times more frequent than national rates in both cohorts. In Japan there is a 3-fold excess of liver cancer mortality in men, which was already detectable and even higher at 15 years than after 22 years of follow-up. In Taiwan, after 12 years of follow-up, there is no excess of liver cancer mortality. Based on these data it was concluded that there is *inadequate evidence* in humans for the carcinogenicity of PCDFs.

Animal Carcinogenicity Data

There are no long-term carcinogenicity studies on PCDFs, but some tumor promotion studies were evaluated in which rats and mice were exposed to some of the congeners following short-duration exposure to known carcinogens (*38–41*). It was concluded that there is *inadequate evidence* in experimental animals for the carcinogenicity of 2,3,7,8-tetrachlorodibenzofuran but there is *limited evidence* in experimental animals for the carcinogenicity of 2,3,4,7,8-pentaCDF and 1,2,3,4,7,8-hexaCDF.

Other Effects

The large number of original references to the data summarized here can be found in *Polychlorinated Dibenzo*-para-*Dioxins and Polychlorinated Dibenzofurans* (*1*). Human exposure to TCDD or other PCDDs because of industrial or accidental exposure or the ingestion of PCDFs in PCB-contaminated rice oil has been associated with chloracne and alterations in liver enzyme levels. Changes in the immune system and glucose metabolism have also been observed in adults. Infants exposed to PCDDs and PCDFs through breast milk exhibit alterations in thyroid hormone levels and possible neurobehavioral and neurologic deficits.

The extraordinary toxicity of TCDD and related 2,3,7,8-substituted PCDDs has been demonstrated in many animal species. The lethal dose of TCDD, however, varies more than 5000-fold between the guinea pig (most sensitive) and the hamster (least sensitive). In all mammalian species tested, lethal doses of TCDD result in delayed death preceded by excessive body weight loss (wasting). Other signs of TCDD intoxication consistent among most species include thymus atrophy; hypertrophy or hyperplasia of hepatic, gastrointestinal, urogenital, and cutaneous epithelia; atrophy of the gonads; subcutaneous edema; and systemic hemorrhage.

Most human studies on reproductive effects of PCDDs concerned paternal exposure, usually long after high exposure had occurred; these provide limited evidence of alterations in hormone levels, sperm characteristics, and immune system. In experimental animals, however, TCDD is both a developmental and reproductive toxicant. The developing embryo/fetus appears to be more sensitive than adult animals to the adverse effects of TCDD. Perturbations of the reproductive system in adult animals require overtly toxic doses. In contrast, effects on the developing organism occur at doses more than two orders of magnitude lower than those that are toxic to the mother. Sensitive targets include the developing reproductive, nervous, and immune systems. In the case of PCDFs, observations of children born after the Yusho (*35,36*) and Yu-cheng (*37*) incidents show signs of intrauterine growth retardation and congenital anomalies at birth and deficit of cognitive development up to 7 years of age. Eight of 39 children exposed *in utero* died after birth. Characteristic effects in survivors include defects in musculoskeletal development and pigmentation and psychomotor delays. Several PCDFs are teratogenic in mice, causing cleft palate and hydronephrosis. 2,3,4,7,8-PentaCDF leads to persistent reproductive effects (reduced sperm count, structural alterations of the female genital tract) following prenatal exposure. 2,3,4,7,8-PentaCDF also promotes the growth of surgically induced endometriosis in mice.

PCDDs cause suppression of both cell-mediated and humoral immunity. Significant reduction of thymus weight and suppression of the activity of cytotoxic T lymphocytes was observed in several species. The numbers of T helper memory cells were decreased in mice, while in marmosets dose-dependent fluctuations of this cell type in peripheral blood were also observed. Alterations of some immune responses can be observed after exposure to doses below 0.1 μg TCDD/kg in mice and nonhuman primates. For example, PCDDs have the potential to suppress resistance to bacterial, viral, and parasitic challenges in mice; a single dose of 10 ng TCDD/kg to mice resulted in an increase in mortality from influenza infection and is the lowest dose that produces an adverse effect yet reported for this compound (*42*).

In addition to these system and organ specific effects of TCDD, exposure of animals leads to an increase in cell proliferation, hyperplasia, and neoplasia in a number of tissues, although it is difficult to define a role based on effective doses for any of these processes (which are normally measured over short-term periods) in neoplasia. Changes in cell growth homeostasis occur during tumor promotion and may be related to alterations in apoptosis, growth factor expression, and growth factor and nuclear hormone receptor levels. It would appear, however, that the primary effects of TCDD and probably other PCDDs and PCDFs are not mediated by a direct-acting genotoxic mode of action.

The toxicity of TCDD to mice genetically segregates with the high-affinity allele for the cytosolic aryl (aromatic) hydrocarbon receptor (AhR), and the relative toxicities of other PCDD congeners are associated with their ability to bind to the receptor. The AhR binding affinities of 2,3,7,8-TCDF and 1,2,3,7,8- and 2,3,4,7,8-pentaCDF are of the same order of magnitude as that observed for TCDD. PCDDs with at least three lateral chlorine atoms bind with some affinity to the AhR. If, as is currently believed, most if not all effects of TCDD arise from an initial high affinity interaction with the AhR, then it would appear that the biochemical and toxicologic consequences of PCDF exposure are the result of a similar mode of action. The limited amount of data available on carcinogenicity for congeners other than TCDD indicate that carcinogenic potency is also proportional to AhR affinity. Based on this evidence all PCDDs and PCDFs are believed to act through a similar mechanism and require an initial binding to the AhR. Binding of TCDD to the AhR results in transcriptional activation of a battery of TCDD-responsive genes, but currently no responsive gene has been proven to have a definitive role in the mechanism of carcinogenesis by TCDD.

Overall Evaluations

After considering the human and animal cancer data together with all of the other experimental data, overall evaluations and classifications were made by the IARC Working Group members. The Working Group concluded that TCDD *is carcinogenic to humans* (group 1).

In making the overall evaluation, the Working Group considered the following supporting evidence:

- TCDD is a multisite carcinogen in experimental animals and has been shown by several lines of evidence to act through a mechanism involving the AhR.

- This receptor is highly conserved in an evolutionary sense and functions the same way in humans as in experimental animals.
- Tissue concentrations are similar both in heavily exposed human populations in which an increased overall cancer risk was observed and in rats exposed to carcinogenic dosage regimens in bioassays.

Other PCDDs *are not classifiable as to their carcinogenicity to humans* (group 3).

Dibenzo-*p*-dioxin *is not classifiable as to its carcinogenicity to humans* (group 3).

PCDFs *are not classifiable as to their carcinogenicity to humans* (group 3).

Discussion

A number of questions arise from these Working Group evaluations, some of which were partially addressed during the IARC 1997 meeting (*1*). The following discussion of these questions has been made without reference to the Working Group members.

Is it unusual to base an epidemiologic evaluation on an aggregation of mortality due to all cancers combined? The usual situation is for mortality from one or a small number of specific tumors to be associated with an exposure. Although tobacco smoking is causally related to deaths from tumors in a number of organs, statistical significance has been repeatedly shown for the relationship with specific individual tumor types. Why should TCDD be treated differently? There are at least two proffered reasons. Few people in a small number of populations have been exposed to high levels of TCDD; hence, if it is a risk factor for several tumor types, perhaps the incidence of a particular tumor type may never be elevated to a level of significance. A parallel, if imperfect, example is environmental tobacco smoke (i.e., smoking-related tumors among nonsmokers). The average relative risk of lung cancer from passive smoking, as estimated by meta-analysis of a large number of epidemiologic studies, is about 1.2 (*43*), whereas among tobacco smokers the relative risk for lung cancer can be 20.0 or more. The U.S. Environmental Protection Agency has performed an informal meta-analysis of TCDD and related chemicals and soft-tissue sarcoma, but the more prominent cancers deserving such treatment must include lung cancer because it is the one that shows overall the highest increased risk. The other proffered reason is that TCDD is a powerful tumor promoter but does not initiate a carcinogenic process itself. In a particular studied population where TCDD is a common exposure, segments of that population may have been exposed to different initiating agents, each with a different organ specificity. Ideally, of course, these factors should have been taken into account in the study analysis for possible confounders. One specific example relevant to these evaluations is the Yusho incident in Japan (*35,36*). Although the exposure in Japan was to PCDFs, not PCDDs, it was considered that the biologic effects of both types of chemicals are mediated by the AhR; consequently, differences in the type of cancer outcome presumably would be due to differences in the initiating agent. Japan is an area of moderately high prevalence of hepatitis virus and both hepatitis B virus (HBV) and hepatitis C virus (HCV) are already recognized liver cancer risk factors (*44*). Accordingly, the action of PCDFs may be to promote the emergence of liver tumors in people carrying HBV or HCV. If this hypothesis is correct, a similar pattern of tumor incidence would also be expected to emerge in Taiwan, which is an area of high HBV and HBC prevalence (*45–48*).

Why was chloracne not used as an indicator of high exposure and then these populations examined for their cancer risk? Frequently, blood or serum concentrations of many PCDDs and PCDFs were available and these were, understandably, considered to be more reliable measures of internal dose. [Note, however, that chloracne occurred in about 80% of Yusho patients in Japan (*35,36*) and 50–75% of Yu-cheng patients in Taiwan (*37*) after the ingestion of contaminated rice oil.] Although this is probably correct, blood levels alone do not give any indication of individual susceptibility. If the consequences of exposure to these compounds are dictated by interaction with the AhR (as argued by many investigators), the development of chloracne in some individuals and not in others may indicate susceptibility differences. These differences may also include cancer development. It is arguable that some post-AhR events could dispose towards chloracne in some individuals, rather than the chemical–receptor interaction itself. Such an argument does nothing to substantiate a greater value of a chemical measurement over a biologic response as an exposure indicator.

If it is indeed correct to state that all biologic actions of these compounds are consequences of their interaction with the AhR, why were the PCDDs other than TCDD and the PCDFs not classified as *possible human carcinogens* (group 2B) when they also interact with the AhR? The binding constants vary over several orders of magnitude, the constant for TCDD being the greatest. Although a theoretical possibility presumably exists for any of these compounds to be carcinogenic, receptor binding of only a few is envisaged to be toxicologically significant. Such an argument runs counter to the objective of the IARC Monographs, which is hazard identification, not risk assessment. However, hazard identification always depends on three basic factors: that an exposure has occurred, that an investigation has been made, and that the investigation had sufficient statistical power to detect a difference between exposed subjects and referents. These principles apply equally to epidemiology and animal experiments, are inescapable and, in experimental situations, the last factor contributes to the increased proportion of tested chemicals that has been identified as carcinogens during the last quarter century (*49*).

The mechanistic support for TCDD being a human carcinogen appears limited to its interaction with the AhR and depends on the presumed involvement of this receptor in most, if not all, toxicologic consequences of exposure and the presence of this receptor with similar titrations in all of the animal species tested. However, no specific subsequent steps were proposed to lead to the development of cancers. Instead, it was considered by the Working Group that the plethora of events that could result from AhR interaction—in particular the transcriptional activation of a number of genes—included currently unidentified steps in a carcinogenic pathway. The Working Group decided that it was more appropriate to apply mechanistic arguments to the evaluation of carcinogenic hazards presented by agents for which substantial bioassay or epidemiologic data were available. In effect, mechanistic considerations were viewed as supportive only in the case of TCDD, for which ample bioassay data and considerable epidemiologic data (which, by themselves, provide *limited evidence* of carcinogenicity to humans) were available.

Is TCDD a highly potent carcinogen? The dose levels required to produce significant increases in tumor incidence in rodents are very low. As a standardized measure of potency, Gold et al. (*50*) calculated that the median toxic dose for TCDD-induced hepatocellular carcinomas in female rats in the Kociba et al.

(*29*) experiment was 0.065 μg/kg body weight/day normalized to a lifespan of 2 years. This is the lowest value of any studied compound. However, the doses required for a carcinogenic effect are also very close to those doses in the same species that produce toxicity in a much shorter time; hence, the demonstrable carcinogenic dose window is narrow. Furthermore, in contrast to certain other carcinogens, the increased proportion of tumor-bearing animals is not great. It is clear from studies of other agents that carcinogenic potency may vary greatly between species (e.g., aflatoxin B_1 in rats and mice) and attempts to extrapolate potency data from rodents to man must be viewed with caution.

With respect to PCDF/PCB contamination of rice oil, has there been adequate explanation of the differences in cancer incidence and mortality between Japan (where liver cancer mortality is currently 3-fold higher in the affected population) and Taiwan (where there is no increase in liver tumors)? The available time for cancer development in Japan is 22 years, compared with only 12 years in Taiwan. Thus, the current epidemiologic evidence is judged to be inadequate but in a few more years this situation may change as the follow-up period for Taiwan gets closer to the current Japanese follow-up. However, two features of the Japanese data suggest that this prediction is not inevitable. Differences in cancer mortality between the Japanese exposed and referent populations are not monotonically increasing with time. One example is mentioned in *Polychlorinated Dibenzo*-para-*Dioxins and Polychlorinated Dibenzofurans* (*1*): the relative risk for liver cancer mortality in men at 15 years was 5.6 ($p < 0.01$), whereas it was 3.4 ($p < 0.01$) at 22 years. Another example is the relative risk for mortality from cancer of the lung, trachea, and bronchus, which at 15 years was 3.3 ($p < 0.01$) but was 1.8 at 22 years (no longer significant) (*35,36*). However, these changes remain consistent with PCDF exposure being a risk factor. If, as is proposed, the principal action of these compounds is tumor promotion, the total cancer burden may not have changed but the emergence of certain cancers may have been accelerated. If this argument is to stand, similar evidence of early emergence of specific cancers, followed by the slower increase of these same cancers in referent populations, should be evident. We are not aware that this has occurred.

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