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Letter

Derivation of permitted daily exposure value for trifluoroacetic acid as an impurity in pharmaceutical products

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ABSTRACT — Trifluoroacetic acid (TFA) has been used for production of pharmaceuticals including recently emerging middle size peptides. TFA has severe local toxicity like skin and respiratory tract irritation due to the strong acidity. Because almost all pharmaceutical products are prepared at neutral pH, derivation of permitted daily exposure (PDE) of TFA from the information with neutralized form could provide useful information on the risk management for protection of patients and production of pharmaceuticals. Sodium TFA caused hepatotoxicity in a rat 90-day. Based on the results of the 90-day study, we respectively proposed PDE for oral, parenteral and inhalation routes as 1.7, 0.005 and 0.84 mg/person/day. The derivation of PDE was done according to the concept described in ICH Q3C(R8) and Q3D(R2).

Key words: Trifluoroacetic acid, PDE, Impurity, Pharmaceutical

INTRODUCTION

Trifluoroacetic acid (TFA) is a strong carboxylic acid commonly used in laboratories and industrial companies. TFA has been used as a raw material and catalyst for manufacture of pharmaceutical products, pesticides and herbicides at industrial sites and in manufacturing. TFA is often used for synthesis of recently emerging middle size peptides. TFA has a corrosive effect on the skin and eyes, respiratory tract irritation due to its strong acidity and classified as hazardous substance with EU and United Nation GHS classification criteria. However, toxicity of pH-adjusted TFA solution was different from acidic effects. Because almost all pharmaceutical products are prepared at neutral pH, derivation of permitted daily exposure (PDE) of TFA from the information with neutralized form could provide useful information on the risk management for protection of patients and production of pharmaceuticals. Here, we proposed PDE for TFA as an impurity in pharmaceutical products based on the open access information provided by international organizations, factsheets, databases and literatures.

MATERIALS AND METHODS

Substance information

Identification

IUPAC Name: trifluoroacetic acid
CAS Number: 76-05-1
EC Number: 200-929-3

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Formula: C2HF3O2
Molecular Weight: 114.02

Chemical and Physical Properties
Appearance: Colorless to almost colorless transparent liquid
Melting Point: -15.4 - -15.3°C
Solubility 20°C: 1,000 - 1,520 g/L
Density 20°C: 1.52 - 1.531
Partition coefficient (Log Pow, 25°C): 0.5 - 0.79
pH 20°C, 10 g/L: 1

Source of toxicological information:

Existing information was searched from information sources including evaluation documents provided by international organizations, factsheets, database and literatures. We found that GHS classification results by ministries concerned, HSDB (Hazardous Substances Data Bank), REACH registered information (REACH Registration Dossier) and GESTIS Substance Database included some accessible data of this substance. Based on the obtained information, toxicity information of this substance was collected and organized.

Information sources surveyed

1. GHS Classification Results by GHS Relevant Ministries (Sourced from: MHLW Site for Occupational Safety)
2. Initial Risk Assessment Report/Chemical Substances Hazard Assessment Report, Chemicals Evaluation and Research Institute, Japan (CERI)/National Institute of Technology and Evaluation (NITE)
3. Japan Existing Chemical Data Base (JECDB), NIHS
4. NITE Toxicity and Eco-toxicity Test Results
5. Ministry of Economy, Trade and Industry (METI) Safety Test Results
6. Public Notice on the Guidelines for Preventing the Impairment of Workers' Health Pursuant to the Provisions in Paragraph 3 of Article 28 of the Industrial Safety and Health Act, MHLW
7. Results of Carcinogenicity Studies Commissioned by MHLW, Japan Bioassay Research Center (JBRC)
8. Environmental Risk Initial Assessment of Chemicals, MOE, Japan
9. Recommendation of Occupational Exposure Limits, Japan Society for Occupational Health (JSOH)
10. OECD SIDS Report (SIDS Initial Assessment Report)
11. Environmental Health Criteria (EHC), IPCS (International Program on Chemical Safety)
12. Concise International Chemical Assessment Document (CICAD), IPCS (International Program on Chemical Safety)
13. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, International Agency for Research on Cancer (IARC)
14. FAO/WHO Joint Expert Committee on Food Additives – Monographs (JECFA Monographs)
15. Risk Assessment Report, EU
16. American Conference of Industrial Hygienists (ACGIH)
17. Integrated Risk Information System (IRIS), U.S. EPA
18. NTP Database
19. NTP Report on Carcinogens (RoC)
20. NTP Technical Report
21. Toxicological Profile, Agency for Toxic Substances and Disease Registry (ATSDR)
22. Priority Substances List Assessment Report, Canadian Environmental Protection Act (CEPA), Environment Canada, Health Canada
23. Australian Department of Health and Aging: Priority Existing Chemical Assessment Report, National Industrial Chemicals Notification and Assessment Scheme (NICNAS)
24. Pesticides "Reregistration Eligibility Decision", U.S. Environmental Protection Agency (EPA)
25. Hazardous Substance Data Bank (HSDB)
26. Test Data of Agricultural Chemicals, Food and Agricultural Materials Inspection Center (FAMIC)
27. Pesticide Safety Information, Japan Crop Protection Association
28. Risk Assessment Reports, Food Safety Commission of Japan
29. Study on the Review of Safety of Existing Food Additives, Ministry of Health, Labor and Welfare (MHLW)
30. NITE CHRIP
31. REACH Registered Substances Information, European Chemicals Agency (ECHA)
32. PubMed
33. PubChem/TOXLINE/TOXNET
34. GESTIS

Derivation of PDE

The concept of PDE derivation described in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q3C(R8) and Q3D(R2) guidelines was applied.

RESULTS AND DISCUSSION

Acute toxicity

It was reported that LD50 in rats by oral administra-

tion was 200 mg/kg (HSDB), but details are unknown. In rats, single gavage administration of 250, 500 and 1,000 mg/kg TFA resulted in 0%, 10% and 100% mortalities, respectively. The LC_{50} values reported for 2-hr inhalation exposure to TFA (vapor) in rats and mice are 10,000 mg/m^3 and 13,500 mg/m^3, respectively (GESTIS, HSDB). Male Wistar rats were exposed to TFA (vapor) at 30, 100 and 300 mg/m^3 by inhalation for 4 hr, no mortality or symptoms were observed up to the highest dose and it was concluded that the NOAEC (local effects) was 300 mg/m^3 (REACH Registration Dossier). For other routes, LD_{50} values of TFA in mice are 1,200 mg/kg for intravenous administration and > 2,000 mg/kg for intraperitoneal administration (Airaksinen and Tammisto (1968), HSDB) were reported.

When TFA itself is applied via the oral, inhalation or dermal route, its strong acidity causes strong local effects (damage to the skin or mucous membranes) at the site of contact, but when administered in the form of pH-adjusted test solutions or the Na salt of TFA (TFA Na) at 7,000 mg/kg, its toxic effects are drastically reduced, as can be seen from the results of acute oral administration studies in rats.

Repeated dose toxicity (Table 1)

In a sub-acute toxicity study (in accordance with OECD TG408, GLP-compliant), rats were fed diets containing TFA Na at concentrations of 160, 1,600 or 16,000 ppm for 90 days. As a result, in males from dose of 1,600 ppm, increases in ALP, AST and ALT activities and histopathological changes on the liver such as centrilobular to panlobular hepatocellular hypertrophy with groundglass appearance of the hepatocellular cytoplasm and decrease of periportal hepatocellular vacuolation were observed. In addition to those changes, increased liver weight (male and female) and high incidence of hepatocellular necrotic foci (male) were observed at 16,000 ppm. In females, slightly lower hemoglobin contents were observed at doses of 1,600 ppm and higher and also slightly lower MCV and MCH values were observed at 16,000 ppm. Therefore, the lowest-observed-adverse-effect-level (LOAEL) and no-observed-adverse-effect-level (NOAEL) were determined to be 1,600 ppm and 160 ppm, respectively, based on the observed effects (histological findings in the liver, changes in hematological and blood chemistry parameters, etc.). Since 160 ppm induced no effects on the liver in males, it was adopted as the NOAEL, and the TFA converted dose was calculated to be 8.4 mg/kg/day (REACH Registration Dossier).

Moreover, it has been reported that the NOEL was 114 mg/kg/day in an 8-day oral administration study of TFA Na in rats (Solomon *et al*. (2016)), but the details are unknown.

Genotoxicity

TFA was negative in a bacterial reverse mutation assay, a gene mutation test using mammalian cultured cells (mouse lymphoma cells) and a chromosomal aberration test using human lymphocytes. There were no data from *in vivo* studies available.

Carcinogenicity

No information regarding carcinogenicity was found for humans or laboratory animals.

Reproductive toxicity (Table 2)

In the developmental toxicity study in rats (in accordance with OECD TG414, GLP-compliant), female rats were treated with TFA at dose of 37.5, 75 and 150 mg/kg/day by oral gavage. At the highest dose of 150 mg/kg/

Table 1. Results of repeated oral administration studies of TFA in laboratory animals.

Study type	Species	Dose	NOAEL/NOEL	Results
14 and 28 days repeated dose toxicity	Rats	Unknown except for 16,000 ppm. (in the diet)	NOAEL= 16,000 ppm (approximately 800 mg/kg/day)* (*: determined by author of this article)	LOAEL: High plasma ALT activity, low total cholesterol and glucose concentrations, high urinary ketone level, high absolute/relative liver weights, no associated histopathological changes (male and female). NOAEL was determined to be 16,000 ppm, which was used as the highest dose in the main study.
90 days sub-chronic toxicity	Rats	0, 160, 1,600, 16,000 ppm Equivalent TFA converted doses: 0/0, 8.4/10.1, 82.3/103.3, 876/1,021 mg/kg/day (in the diet)	NOAEL = 160 ppm (approximately 8.4 mg/kg/day)	1,600 ppm and higher: Centrilobular to panlobular hepatocellular hypertrophy with the ground glass appearance of the hepatocellular cytoplasm (slight to moderate), decrease of periportal hepatocellular vacuolation (male), increases in ALP. AST and ALT activities (male), slightly lower hemoglobin content (female) 16,000 ppm: Reduction in body weight gain (male and female), above-mentioned hepatocellular findings (female), increased liver weight (male and female), high incidence of hepatocellular necrotic foci (male), slightly lower MCV and MCH values (female)
8 days repeated dose toxicty	Rat	ND	NOEL = 114 mg/kg/day	ND

ND: No data.

Table 2. Results of oral reproductive toxicity studies in laboratory animals.

Study type	Species	Dose	NOAEL/NOEL	Results
Developmental toxicity	Rat, pregnant female	0, 37.5, 75, 150 mg/kg/day (Oral gavage) Treatment: GD6-GD19	NOAEL = 150 mg/kg/day (maternal animals and fetuses) NOEL = 75 mg/kg/day (maternal animals), 150 mg/kg/day (fetuses)	Maternal animals: 150 mg/kg: slight increases of liver and kidney weights Fetuses: No abnormalities
Developmental toxicity	Rat, pregnant female	0, 75, 150 mg/kg/day (Oral gavage) Treatment: GD10-GD20	Not mentioned.	Maternal animals: 75 mg/kg and higher: Increases of absolute and relative liver weights, decrease of urinary GGT Offspring: No effects on neonatal survival or postnatal growth. 75 mg/kg and higher: Increases in serum glutamate dehydrogenase and AST activity (postnatal day 3) 150 mg/kg: Increase in urinary β2-microglobulin, decrease in urinary GGT (by postnatal day 12) The above changes were no longer observed on postnatal day 49.
Developmental toxicity	Rabbit, pregnant female	180, 375, 750 mg/kg/day (Oral gavage) Treatment: GD6-GD28	NOAEL = 180 mg/kg/day (maternal animals) Based on the maternal liver pathology of bile duct hyperplasia/fibrosis at 375 mg/kg/day and more. NOAEL = < 180 mg/kg/day (fetal animals) Due to the fetal abnormalities	Maternal: 180 mg/kg/day and higher: Decreased adjusted body weight gain and food consumption, increases of relative liver weights, bile duct hyperplasia/fibrosis (moderate severity at 375 and 750 mg/kg/day) and minimal generalized hepatocellular hypertrophy Offspring: 375 and higher; Reduced mean fetal weights. Increased incidence of eyes abnormalities (Multiple folded retina, Absent aqueous/vitreous humour, single instances of retina ruptured into surrounding tissues, small/misshapen lens and microphthalmia). 180 mg/kg/day: One fetus had microphthalmia, with multiple folded retina and absent aqueous/vitreous humour.
Extended one-generation reproductive performance study (Dose range finding)	Rats	1400, 3400, and 8400 ppm (100, 250 and 650 mg/kg/day): (in the diet) Treatment: F0 females: from Day 6 after mating up to weaning of the F1 offspring F1 animals: from mid lactation until Day 35 of age. (Dietary levels were reduced to 700, 1400 and 4200 ppm during lactation and for F1 offspring)	Not mentioned	Maternal animals: 8400 (4200) ppm: Low overall body weight gain and food consumption (GD6 to GD20, During lactation). 1400 (700) ppm and higher: Low absolute body weight (During lactation), Increased relative liver weight F1 Responses: 8400 (4200) ppm: Low live birth index, low mean litter size, Low body weight gain (LD1-21) 3400 (1700) ppm and higher: food consumption (Day 21 to Day 34 of age) 1400 (700) ppm and higher: High relative liver weight
Extended one-generation reproductive toxicity	Rats	120, 600 and 3000 ppm (10, 50 and 250 mg/kg/day): (in the diet) Treatment: F0 males: for ten weeks before pairing up to necropsy after litters were weaned. F0 females: for ten weeks before pairing, throughout pairing up to necropsy on Day 28 of lactation F1 animals: from PND 21 to PND 35 (Dietary levels were reduced to 60, 300 and 1500 ppm during lactation and for F1 offspring)	NOAEL = 250 mg/kg/day for reproductive performance/offspring development and general systemic toxicity. LOEL = 10 mg/kg/day Based on low plasma glucose, non-esterified fatty acids, triglyceride and bilirubin levels in the F0 and/or F1 males and/or females.	Maternal animals: Low plasma glucose non-esterified fatty acids and triglyceride concentrations and bilirubin plasma concentrations at all dose levels in males and/or females. High plasma sodium levels and low potassium levels at 3000/1500 ppm in males or females. Low mean serum T4 concentrations at 3000/1500 ppm in males and females. High relative liver weight at 3000/1500 ppm in males and females. High kidney weights at 3000/1500 ppm in males and females and at 600 ppm in females. Gland dilatation in the fundic portion of the glandular stomachs at 600/300 and 3000/1500 ppm in females. F1 Responses: Gland dilatation and decreased secretion in the mucous neck cells in the fundic portion of the glandular stomachs at 1500/3000 ppm in females. High relative liver weight at 3000/1500 ppm in male and females. Low plasma glucose, non-esterified fatty acids and triglyceride levels in males and/or females. Low bilirubin levels at 600/300 or 3000/1500 ppm in males and at 3000/1500 ppm in females. High plasma sodium levels and low potassium levels at 3000/1500 ppm. Low absolute testes weights in males at 3000/1500 ppm. Low mean serum T4 concentrations at 1500 ppm in males and females.

GD: Gestation day, PND: postnatal day

day, slight increases of liver and kidney weights (not considered as toxic effects) were observed in the mothers, but no abnormalities were found in the fetuses. In conclusion, the maternal and the embryo-fetal NOAEL were established at 150 mg/kg/day. Due to the non-adverse, test article-related organ weight increases, the maternal and embryo-fetal no-observed-effect-levels (NOEL) were established at 75 mg/kg/day (maternal) and 150 mg/kg/day (embryo-fetal).

In the developmental toxicity study in rabbits (in accordance with OECD TG414, GLP-compliant), female rabbits were treated with TFA at dose of 180, 375 and 750 mg/kg/day by oral gavage. At 180 mg/kg/day and higher, decreased adjusted body weight gain and food consumption, increases of relative liver weights, bile duct hyperplasia/fibrosis (moderate severity at 375 and 750 mg/kg/day) and minimal generalized hepatocellular hypertrophy were noted. In the fetuses, at 180 mg/kg/day and higher, increased incidence of eyes abnormalities (multiple folded retina, absent aqueous/vitreous humour and microphthalmia). In conclusion, the maternal and the embryo-fetal NOAEL were established at 180 mg/kg/day and less than 180 mg/kg/day, respectively. (REACH Registration Dossier).

In the extended one-generation reproductive toxicity study (120, 600 and 3000 ppm (10, 50 and 250 mg/kg/day), as the maternal toxicity, low plasma glucose non-esterified fatty acids and triglyceride and bilirubin levels were noted at all dose levels. At high dose, changes in plasma electrolyte levels and low serum T4 levels were noted in males and females. In the pathology, high relative liver and kidney weights and gland dilatation in the fundic portion of the glandular stomachs were observed at middle dose and more. Generally similar changes were observed in F1 animals at the same dose level as in the dams. The NOAEL were established at 250 mg/kg/day for the F0 and F1 animals. (REACH Registration Dossier)

Female rats were administered with TFA by oral gavage on gestational days 10-20, and the spontaneously delivered pups were sacrificed on postnatal days 3, 12 and 49 to study the effects (effects on hepatic and renal functions) of in utero exposure. As a result, exposure of maternal rats to doses up to 150 mg/kg/day did not affect the neonatal survival or postnatal growth of the pups, but changes indicative of effects on hepatic function (increases in serum glutamate dehydrogenase and AST activity) and renal function (increase in urinary excretion of β_2-microglobulin) were observed by postnatal day 12. However, these changes were no longer observed on postnatal day 49. (Saillenfait *et al*. (1996), HSDB).

Skin/Eye irritation

In humans, there are few reported cases of skin damage and burns caused by accidental dermal exposure to TFA.

In laboratory animals, TFA caused formation of ulcers and scarring at the site of application on rabbit skin (GESTIS). Regarding irritative/corrosive effects on the eyes, there are no human reports or standard animal studies. Nevertheless, TFA is corrosive to the skin and caused corneal opacity in a study of acute inhalation exposure in rats and mice, so it is considered that the vapor of TFA may cause severe irritation or corrosive effects to the eyes (GESTIS).

An aqueous 10% solution of TFA has a strong acidity with a pH of 0.45 and is classified as Skin Corr. 1A in EU (ECHA C&L Inventory). In line with the United Nation GHS classification criteria, Japan also classifies this substance under Category 1 for skin corrosion and Category 1 for eye damage/irritation (GHS Classification Guidance for the Japanese Government 2013 Edition).

Based on the above information, it was concluded that this substance is corrosive to the skin and eyes of humans and animals.

Skin sensitization

Regarding skin sensitization, in humans, a man exposed to several substances including TFA for about 18 months developed a recurrent rash on his neck and arms. Two patch tests were performed with 1% solutions of 5 chemicals including TFA, and positive reactions were observed for TFA in both tests. Although other substances also produced positive reactions, the authors of the original report concluded that the allergen with the highest association with the patient was TFA and diagnosed the case as allergic contact dermatitis triggered by TFA (Byun *et al*. (2013)).

In laboratory animals, there are no reports of skin sensitization by TFA.

Safety pharmacology

No relevant data was available.

Bioavailability

No relevant data was available.

Other *in vitro* safety data

No relevant data was available.

Experience of human exposure

No relevant data was available.

Derivation of PDE for oral route

Critical effect

As the key studies for setting PDE value, the 90-day repeated dose toxicity study conducted by dietary administration of TFA and the developmental toxicity study conducted by oral gavage of TFA were selected. As shown the following, histopathological changes on liver in the 90-day repeated dose toxicity study was the critical leading effect of TFA for the purpose of this assessment and was used as the basis for setting PDE value.

Scenario 1: On the basis of repeated dose toxicity

In the 90-day repeated dose study, NOAEL was determined to be 8.4 mg/kg/day at which no effects on the liver were observed. At the LOAEL for males (1,600 ppm), the observed effects were limited to hepatocellular hypertrophy histologically associated with the ground glass appearance of the hepatocyte and increases in serum measurements of liver-derived enzymes (ALP, AST, ALT).

PDE oral = 8.4 mg/kg/day x 50 kg / (F1 x F2 x F3 x F4 x F5) = 1.68 ~ 1.7 mg/person/day

Modification factor applied:
F1 = 5 for extrapolation from rat to human
F2 = 10 for variability between individuals
F3 = 5 for study duration of 90 days with rats
F4 = 1 for severity of toxicity
F5 = 1, we regarded the starting point as NOEL

Scenario 2: On the basis of reproductive toxicity

Regarding NOAEL/NOEL for developmental toxicity, based on the results of developmental toxicity study toxicity study conducted by orally administering TFA to pregnant rats (in accordance with OECD TG414, GLP-compliant) in which doses up to 150 mg/kg/day had slight effects (slight increases of liver and kidney weights) in the mothers but no developmental effects on the fetuses, no-observed-effect-levels (NOEL) were established at 75 mg/kg/day (maternal) and 150 mg/kg/day (embryo-fetal).

PDE oral = 180 mg/kg/day x 50 kg / (F1 x F2 x F3 x F4 x F5) = 36.0 mg/person/day

F1 = 2.5 for extrapolation from rabbit to human
F2 = 10 for variability between individuals
F3 = 1 for study duration of gestational period
F4 = 5 for a teratogenic effect with maternal toxicity
F5 = 2 for conversion of the starting point to NOEL, effects were seen in a small number of fetus (one fetus of one litter)

Because PDE derived from the 90-day repeated dose toxicity study was lower than that from developmental toxicity study, 1.7 mg/person/day was applied as the PDE for oral route.

Derivation of PDE for parenteral route

There is a report of skin sensitization in a human experience with a mixture including TFA. No further support for sensitizing effects of TFA was found. Strong acidity is destructive to protein conformation, which may cause immunogenicity and antigenicity. There was no available information of sensitization with neutralized TFA.

Oral absorption of TFA was unclear. When radiolabeled trichloroacetic acid (TCA), which have the same carbonic structure as acetic acid, was orally administered to rats or mice, 57-72% of the radio activity was retrieved in urine (IARC 2014, IARC Monographs on the evaluation of carcinogenic risks to humans. Vol 106). Assuming that oral absorption of TFA was 50%, parenteral PDE was calculated.

PDE parenteral = PDE oral x 50/100 = 1.68 x 50/100 = 0.84 mg/person/day

However, we conservatively propose 5 μg/day parenteral PDE for TFE in accordance with the proposal of PQRI (Paskiet *et al*., 2013, PDA J Pharm Sci Tech, 67, 430-447) for sensitizers because the mixture containing TFA was reported to be a sensitizer in human.

Derivation of PDE for inhalation route

TFA is a corrosive substance causing strong irritation in the airway due to the strong acidity. The NOAEC (local) of 300 mg/m^3 established in the rat acute inhalation toxicity study was reported. There was no repeated toxicity study of inhalation exposure. Regarding neutralized TFA, we proposed the same PDE value for inhalation route as parenteral PDE.

PDE inhalation = 0.84 mg/person/day

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