# Perfluorooctanoic acid (PFOA) AND its inorganic salts (EXCluding APFO)

| CAS numbers: | Carboxylic acid (PFOA): 335-67-1  Sodium carboxylate (NaPFO): 335-95-5  Potassium carboxylate (KPFO): 2395-00-8 |
| --- | --- |
| Synonyms: | PFAS, PFOS |
| Chemical formula: | PFOA: C8HF15O2  NaPFO: C8F15O2Na  KPFO: C8F15O2K |

Workplace exposure standard (interim)

| TWA: | **—** |
| --- | --- |
| STEL: | **—** |
| Peak limitation: | **—** |
| Notations: | **Carc 2, Sk.** |
| IDLH: | — |
| **Sampling and analysis:** The recommended value is quantifiable through available sampling and analysis techniques. | |

## Recommendation and basis for workplace exposure standard

A TWA is not recommended due to a lack of reliable human inhalation exposure data.

Given the limited data available from the primary sources, it is recommended that a review of additional sources be conducted at the next scheduled review.

## Discussion and conclusions

Perfluorooctanoic acid (PFOA) and its inorganic salts are used in the production of non-stick cookware, fluoropolymer paints, firefighting foams and in weather resistant textile coatings. This evaluation is for perfluorooctanoic acid (PFOA) and its inorganic salts. Evaluation of ammonium perfluorooctanoate (APFO) is included in the APFO report.

The critical effect of exposure in animals is liver damage as reported in chronic and sub-chronic feeding studies. Carcinogenicity endpoints observed in animals are not confirmed in humans.

Human data are limited to epidemiological studies, which lack inhalational exposure information and generally infer exposure from serum PFOA levels. The results of these studies are equivocal for liver, kidney and testicular toxicity, including carcinogenesis. However, there is non-linear correlation between exposure and carcinogenic effects in these studies, which means the results are not reliable for carcinogenic risk in humans (DFG, 2006; HCOTN, 2013; IARC, 2017). The highest average serum level of 6.4 mg/L PFOA is reported in workers of a production plant (DFG, 2006). A NOAEL of 0.06 mg/kg/day for liver cell hypertrophy is reported in a sub-chronic feeding study in rats. No experimentally determined NOAEL is available for monkeys. A NOAEL of 7 mg/L serum PFOA for liver toxicity in monkeys is extrapolated from toxicokinetic data in rats by DFG (2006) and assumed to be representative of the NOAEL in humans. This blood level is calculated to be associated with an air concentration of 0.005 mg/m3 and likely represents a conservative estimate (DFG, 2006). It should be noted that this bioavailability and systemic toxicity data is not derived from inhalation toxicity studies.

Additionally, there are considerable differences between reported serum half-lives of PFOA in various species (DFG, 2006). This discrepancy further complicates the comparison of animal and human toxicity data. Carcinogenic activity is confirmed in chronically fed rodents. However, the presumed mechanism of action is of unknown relevance to humans (HCOTN, 2013; IARC, 2017).

The uncommon approach used to derive the DFG (2006) MAK indicates considerable uncertainty in the available dataset. Specifically, a NOAEL for liver toxicity in humans or monkeys is not directly determined and large interspecies variations in half-life of PFOA are not understood (DFG, 2006). Due to these uncertainties with the single primary source TWA value and in the absence of robust quantitative human exposure data, a TWA is not recommended. A review of additional data sources is recommended at subsequent reviews to identify data on human inhalational toxicity and carcinogenic activity.

Additionally, the available toxicological database indicates that inorganic PFOA salts, including APFO, are converted to PFOA under physiological conditions and the PFOA anion is of primary toxicological concern (DFG, 2006; NICNAS, 2015). For this reason, the inclusion of APFO in the grouped assessment of PFOA and its inorganic salts should also be considered at the next scheduled review of the WES.

## Recommendation for notations

Classified as a category 2 carcinogen according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS). There are inconsistencies in the carcinogenicity notation across the available source material. Further review of this notation is recommended during the next scheduled review.

Not classified as a skin sensitiser or respiratory sensitiser according to the GHS.

A skin notation is recommended due to evidence of adverse systemic effects from dermal absorption in animals.

# Appendix

### Primary sources with reports

| Source Year set Standard |
| --- |
| SWA NA NA | |
| No report for PFOA (refer to APFO evaluation report for details on APFO). |
| ACGIH NA NA |
| No report for PFOA (refer to APFO evaluation report for details on APFO). |
| DFG 2005 MAK: 0.005 mg/m3 (inhalable fraction) |
| Summary of information:  Absorbed APFO is converted to- and distributed through the organism as PFOA under physiological conditions; exposure data for APFO and PFOA are used interchangeably for DFG evaluation.  Liver damage is the critical effect.  Systemic effects on liver, testes, mammary glands and pancreas observed in animals may occur in humans at high concentrations. However, it has not been confirmed by epidemiological studies of workers exposed to APFO.  Epidemiological data insufficient to derive a MAK.   * The derivation of the MAK is based on a 13-wk rat study with a NOAEL of 0.06 mg/kg/d for liver cell hypertrophy and related to serum concentrations of 7 mg/L * Due to large differences in half-life between rats and humans, it is more relevant the MAK be based on serum concentrations rather than a dose related to bw * Correlation of serum PFOA concentrations with liver cell hypertrophy in rats and monkeys indicates these species react similarly to this endpoint * the LOAEL of 41 mg/L for a liver weight increase of 5% in rats corresponds to an 8% increase in liver weight in monkeys * Linear extrapolation to 7 mg/L serum PFOA for monkeys corresponds to a liver PFOA concentration (0.57 mg PFOA/kg liver) associated with an increase in the relative liver weight of 1% * 7 mg/L is regarded as the NOAEL for monkeys * Assuming linear kinetics, the NOAEL of 7 mg/L is applied to humans and is likely a conservative estimate and no further safety factors are applied.   The MAK is calculated as an air concentration exposure (cair) of 0.005 mg/m3 that would result in a serum concentration (cblood) of 7 mg/L in humans using the following formula:  The calculation is based on the following assumptions:   * a half-life (t1/2) of 3.8 yr * distribution volume of 0.2 L/kg * 100% retention * respiratory volume of 10 m3 * 70 kg bw.   Not classified as carcinogenic in humans (category 4) due to absence of effects in organs for which tumorigenicity is observed in rats with a non-linear dose-response.  Skin notation recommended based on systemic uptake from dermal absorption in rats.  Human data:   * Serum t1/2 ≈2.5 yr in 1 female production worker with initial serum PFOA of 70 mg/L, which decreased to 39 mg/L in 18 mo after transferral to PFOA-free work area   + PFOA excretion measured in urine; initially 387 µg/d which decreased to 80 µg/d after 14 mo * Average t1/2 of 3.8 yr in retired production works (n=27, employed for average of 27.7 yr) reported in 2-phase study:   + in phase1, serum levels monitored every 6 mo for 5 yr and a median t1/2 of 344 d reported   + a mean t1/2 of 4.37 yr second phase of monitoring reported in 9 of the 27 initial subjects with 4 serum measurements every 180 d to account for errors noted in the first phase   + age, BMI, number of years employed and number of years since retirement had no influence on t1/2   + one subject excluded from final analysis due to likely additional exposure during the study   + DFG acknowledges considerable difference in t1/2 in humans of this study compared with those in animals, but provides no further details on this discrepancy * Serum PFOA concentrations of exposed production workers at various plants were:   + Cottage Grove (Minnesota) * mean of 6.4 mg/L in 1997 (not stated if GM or AM) * GM of 0.42 and 0.85 mg/L in males and females, respectively in 2000 (AM not provided) * follow-up cross-sectional study (n=115) reported no effect on liver function or metabolic parameters * no increase in SMR in retrospective mortality study (n=749 females; n=2,788 males)   + Serum levels were 0.33 and 1.13 mg/L (GM), and 0.84 and 1.78 mg/L (AM), respectively in 2 other plants, Antwerp (Belgium) and Decatur (Alabama) in 2000 * No exposure-related effects in APFO production workers (n≈300) exposed for ≥1 year at 0.01–7.6 mg/m3   + serum levels ranged from 0.04–71.0 mg/L in exposed workers and 0.01‑0.08 mg/L in controls   + correlation of serum levels with air concentrations unreliable because the study design was inadequate * Serum levels in general population estimated from 3 studies at 4–5 µg/L (GM) were unaffected by age with no evidence for accumulation found in elderly compared with young subjects.   Animal data:   * Half-life of 20–30 d in monkeys; 10 h–7 d in rats (faster elimination in females) * Reversible liver toxicity at 200 mg/kg/d in dermal application study (rats, 6 h/d, 5 d/wk, 2 wk) * NOAEC of 1 mg/m3 APFO for reversible liver weight increase and microscopic liver changes (rats, 6 h/d, 5 d/wk, 2 wk) with corresponding LOAEC of 8 mg/m3;   + reduced bw at 84 mg/m3 * NOAEL of 0.06 mg/kg/d (7 mg/L serum PFOA) for liver cell hypertrophy and reversible increased liver weight (5%) reported in sub-chronic feeding study (rats, 90 d)   + LOAEL of 0.64 mg/kg/d (41 mg/L serum PFOA)   + no other microscopic changes at the maximum concentration of 6.5 mg/kg/d (138 mg/L serum PFOA) * Increased liver weights (20%) and evidence of peroxisome proliferation in the liver at both 3 mg/kg/d (low dose) and 10 mg/kg/d (mid dose) reported in 2 oral dose studies (monkeys, 13 and 26 wk)   + maximum dose of 30 mg/kg/d discontinued due to high toxicity (anorexia, vomiting, hypocellular bone marrow, spleen atrophy)   + in 26-wk study, 3 and 10 mg/kg/d corresponded to a non-linear concentration of 77 and 86 mg/L serum PFOA, and 19 and 22% increased liver weight, respectively * Increased incidence of liver, adrenal, pancreatic and Leydig cell cancers reported in two chronic feeding studies at 0, 1.5, 13.6 and 15 mg/kg/d (rats, 2 yr).   + decreased bw reported in both studies at 13.6 and 15 mg/kg/d and increased mortality at 13.6 mg/kg/d reported in one study   + NOAEL of 1.5 mg/kg/d:   + tumour promoting effect potentially due to impairment of fatty acid metabolism and subsequent over expression of peroxisome proliferation genes in liver (rats, mice) * NOAEL of 30 mg/kg/d and 10 mg/kg/d for fertility and developmental toxicity, respectively, for reduced bw and viability in 2-genrepeat gavage study (rats)   + F0 exposed from for ≈30 d from wk 6–10 of age   + F1 and F2 exposed from wk 3 of age onwards   + increased liver and kidney weights reported in all males at doses ≥1 mg/kg/d (lowest tested dose)   + considered a LOAEL for general toxicity by cited article * NOAEL of 5 mg/kg/d for increased incidence of extra ribs and 50 mg/kg/d for dams (highest tested dose) in developmental gavage study (rabbits, GD 6–18) * Not considered genotoxic based on negative results *in vitro* with bacteria and Chinese hamster ovarian cells and *in vivo* with mice.   Insufficient data to recommend a sensitiser notation. |
| SCOEL NA NA |
| No report. |
| OARS/AIHA NA NA |
| No report. |
| HCOTN 2013 Not established |
| Summary of additional information:  Available report only assesses carcinogenic potential of PFOA/APFO; no OEL derivation/recommendation is considered or derived.  Available data are insufficient to assess carcinogenicity in humans (category 3).  Human data:   * Several epidemiological studies of production plant workers, exposed primarily to APFO (6), nearby populations exposed *via* drinking water (2), and general population (3) were considered in the assessment:   + overall no specific cancer type is consistently associated with exposure   + a slight, but statistically significant, excess in kidney cancer considered of highest concern for workers exposed at the highest exposure quartile in one population study (exposure details not specified) * Workplace studies (sample sizes n≈3,000–6,000):   + SMR for all causes, including cancer, generally reported near unity in all studies   + inconsistencies in categorisation of exposure groups complicates comparison of reported studies   + SMR for the internal control groups used in 2 studies were markedly less than one whereas studies of exposed workers reported SMR about one consistent with regional statistics   + non-significant increases in SMR and small number of deaths for liver, kidney, pancreas, testicular, and breast cancers reported in one study of the West Virginia production plant cf populations of the US, West Virginia, and company employees from 8 states     - no increased mortality in reported   + increased SMR from prostate cancer associated with length of employment reported in one study limited to small number of cases used to derive mortality rates and mixed exposure of workers to other carcinogenic substances (benzene, asbestos) * Nearby population studies (sample sizes n≈25,000–32,000):   + increased PFOA serum levels associated with testicular, kidney, prostate, and ovarian cancers, and NHL from drinking water exposure reported in case-control study limited due to uncertainty about exposure by drinking water   + exposure-dependent increased risk of kidney and testicular cancer associated with exposure to PFOA in drinking water limited due to biases from self-reporting of participants, quality of medical records used in the study, lack of a control population, and inconsistency of symptoms of higher exposed workers * General population studies (sample sizes n=31 and 57,000):   + no liner correlation between PFOA concentration and cancer; no impact of gender   + PFOA plasma levels of 7 µg/L in Danish general population not associated with excess risk of prostate, bladder, pancreatic or liver cancers     - mean plasma concentrations in general population significantly lower than exposed workers, which had a plasma concentration of 0.3–5.2 mg/L.   Animal data:   * Insufficient evidence for carcinogenicity in animals assessed from 2 chronic feeding studies with rats and a repeat oral dose study with monkeys (all cited in DFG, 2006):   + tumours reported in rats considered benign. Liver cell tumours likely caused by peroxisome proliferation (also cited in DFG, 2006)   + Leydig cell and pancreatic tumours in rats not observed in monkeys and considered a result of rodent-specific hormone metabolism   + repeat oral dose study with monkeys considered too short (6 mo) to assess carcinogenic potential * Overall considered non-genotoxic based on limited *in vitro* and *in vivo* studies; agency attributes isolated positive results *in vitro* to indirect effects caused by generation of ROS. |

### Secondary source reports relied upon

| Source |  | Year | Additional information |
| --- | --- | --- | --- |
| NICNAS |  | 2015 | * PFOA assessment grouped with APFO as both substances release the perfluorooctanoate anion in solution, which is of primary concern for the assessment * APFO not irritating to skin, no data for PFOA (rabbits, occluded patch, 24 h); NICNAS notes irritant profile cannot be extrapolated for PFOA due to its strong acidity * NOAEL of 10 mg/m3 for developmental toxicity reduced body weight (rats) |
| IARC |  | 2017 | * *In vitro* dermal permeability coefficient: 9.49 x 10-7 cm/h (human skin) * Liver considered primary target organ in humans * Overall moderate evidence for potential carcinogenic mechanisms of action observed in animals to be operative in humans based on:   + strong evidence for liver carcinogenicity in animal studies likely induced by peroxisome proliferation related mechanism   + weak evidence for carcinogenicity of reproductive organs in animals caused by interference with hormone metabolism * Increased risk of kidney and testicular cancer reported in studies of high exposure populations near production plants (also cited in HCOTN, 2013) considered credible, but limited due to potential sampling bias, confounders, and, in the case of testicular cancer, small number of incidences * Moderate evidence for overall non-genotoxicity based on large number of negative results from direct genotoxicity assays, with some indication for indirect DNA damage caused by oxidative stress * Overall, possibly carcinogenic to humans (Group 2B). |
| OECD |  | 2008 | * PFOA and APFO evaluated in grouped assessment, other inorganic salts are not considered * PFOA and APFO are metabolically equivalent, distributed primarily extracellularly to liver, serum, and kidney and do not partition to the adipose tissue * Sufficient evidence for induction of peroxisome proliferation related responses in the liver, which cause toxicity and carcinogenicity * Negative mutagenicity *in vivo*, positive results *in vitro* in mammalian cells when tested with metabolic activation. |

### Carcinogenicity — non-threshold based genotoxic carcinogens

| Is the chemical mutagenic? | No |
| --- | --- |
| **The chemical is not a non-threshold based genotoxic carcinogen.** |  |

## Notations

| Source | Notations |
| --- | --- |
| SWA | NA |
| HCIS | Carcinogenicity – category 2 |
| NICNAS | Carc. Cat. 3 |
| EU Annex | Carcinogenicity – category 2 |
| ECHA | Carc. 2 |
| ACGIH | NA |
| DFG | Carcinogenicity – 4, H (skin) |
| SCOEL | NA |
| HCOTN | Carcinogenicity – category 3 |
| IARC | Carcinogenicity – Group 2B |
| US NIOSH | NA |

NA = not applicable (a recommendation has not been made by this Agency); — = the Agency has assessed available data for this chemical but has not recommended any notations

### Skin notation assessment

| Calculation |
| --- |
| |  |  |  |  |  | | --- | --- | --- | --- | --- | | Adverse effects in human case study: |  |  |  |  | | Dermal LD50 ≤1000 mg/kg: | no |  |  |  | | Dermal repeat-dose NOAEL ≤200 mg/kg: | yes | 3.00 |  |  | | Dermal LD50/Inhalation LD50 <10: |  |  |  |  | | *In vivo* dermal absorption rate >10%: |  |  |  |  | | Estimated dermal exposure at WES >10%: |  |  |  |  | |  |  | 3 |  | **consider assigning a skin notation** | |

### IDLH

| Is there a suitable IDLH value available? | No |
| --- | --- |

## Additional information

| Molecular weight: | 414.07 |
| --- | --- |
| Conversion factors at 25°C and 101.3 kPa: | 1 ppm = 16.94 mg/m3; 1 mg/m3 = 0.059 ppm |
| This chemical is used as a pesticide: |  |
| This chemical is a biological product: |  |
| This chemical is a by-product of a process: |  |
| A biological exposure index has been recommended by these agencies: | ACGIH  DFG  SCOEL |

## Workplace exposure standard history

| Year | Standard |
| --- | --- |
| Click here to enter year |  |

## References

American Conference of Industrial Hygienists (ACGIH®) (2018) TLVs® and BEIs® with 7th Edition Documentation, CD-ROM, Single User Version. Copyright 2018. Reprinted with permission. See the [*TLVs® and BEIs® Guidelines section*](http://www.acgih.org/tlv-bei-guidelines/policies-procedures-presentations) on the ACGIH website.

Deutsche Forschungsgemeinschaft (DFG) (2012) Perfluorooctanoic acid and its inorganic salts – MAK value documentation.

European Chemicals Agency (ECHA) (2020) Pentadecafluorooctanoic acid– REACH assessment.

Tenth Adaptation to Technical Progress Commission Regulation (EU) No 2017/776 amending, for the purposes of its adaptation to technical and scientific progress, Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures (the CLP Regulation).

International Agency for Research on Cancer (IARC) (2017), Volume 110, Some Chemicals Used as Solvents and in Polymer Manufacture. IARC Monographs on the evaluation of the carcinogenic risk to humans.

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (2015) Perfluorooctanoic Acid (PFOA) and its Direct Precursors: Human health tier II assessment – IMAP report.