Evaluation of PFOA and PFOS for human health standards

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WISCONSIN DEPT. OF NATURAL RESOURCES

Today’s presentation

Basis for human health standards

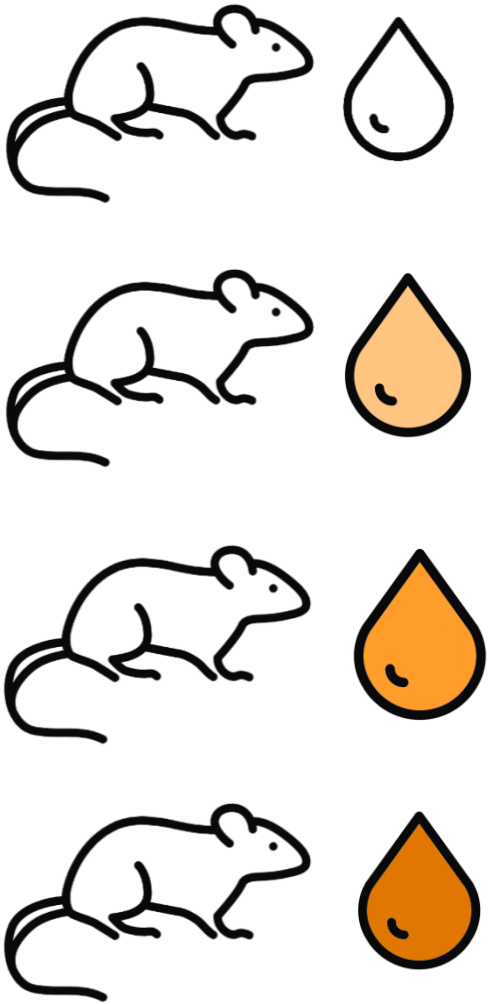
Groundwater standard process

Recommended groundwater standard for PFOA

Recommended groundwater standard for PFOS

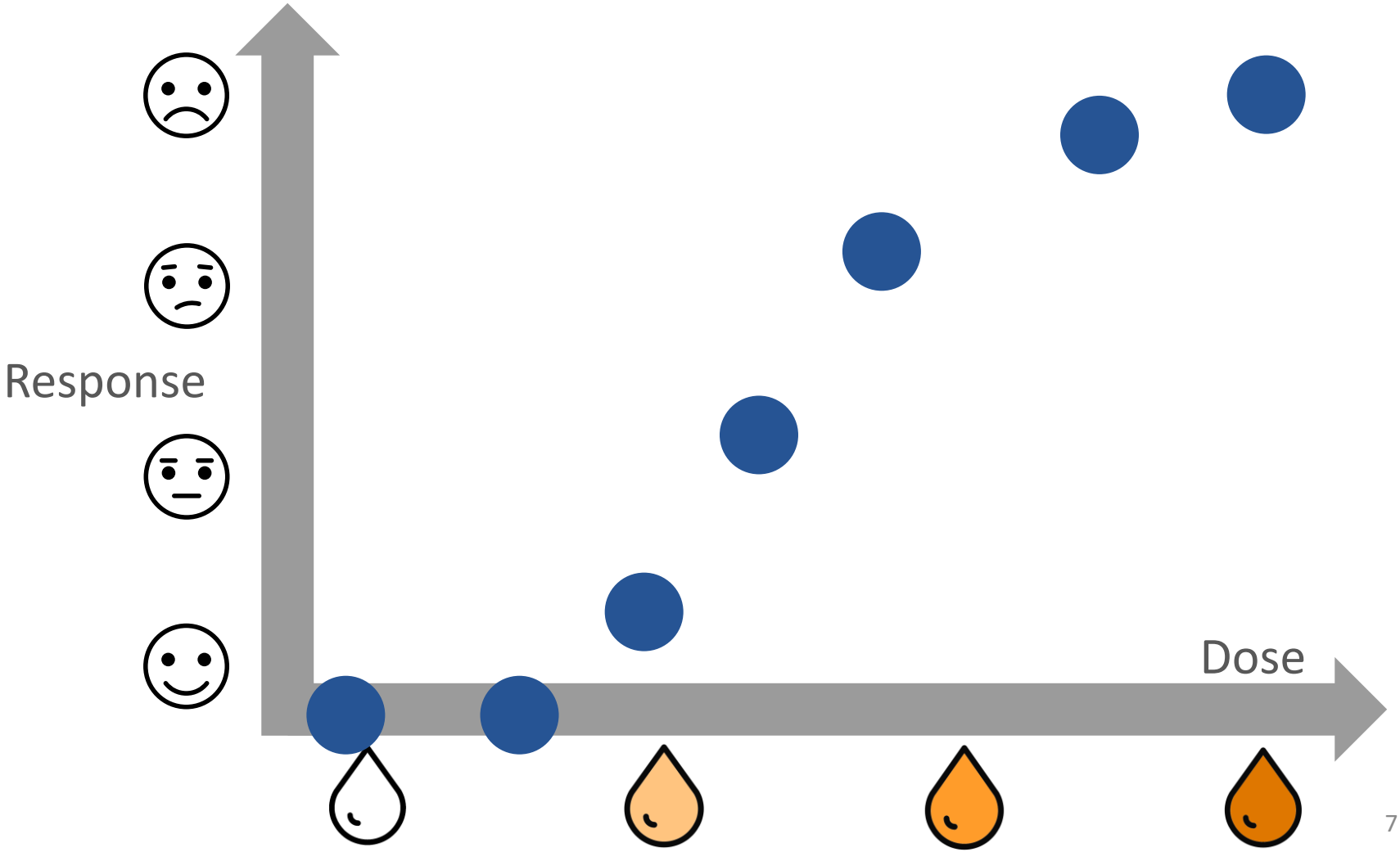
Standards are set to protect health of Wisconsin residents.

Most human health standards are based on toxicology studies conducted in research animals.



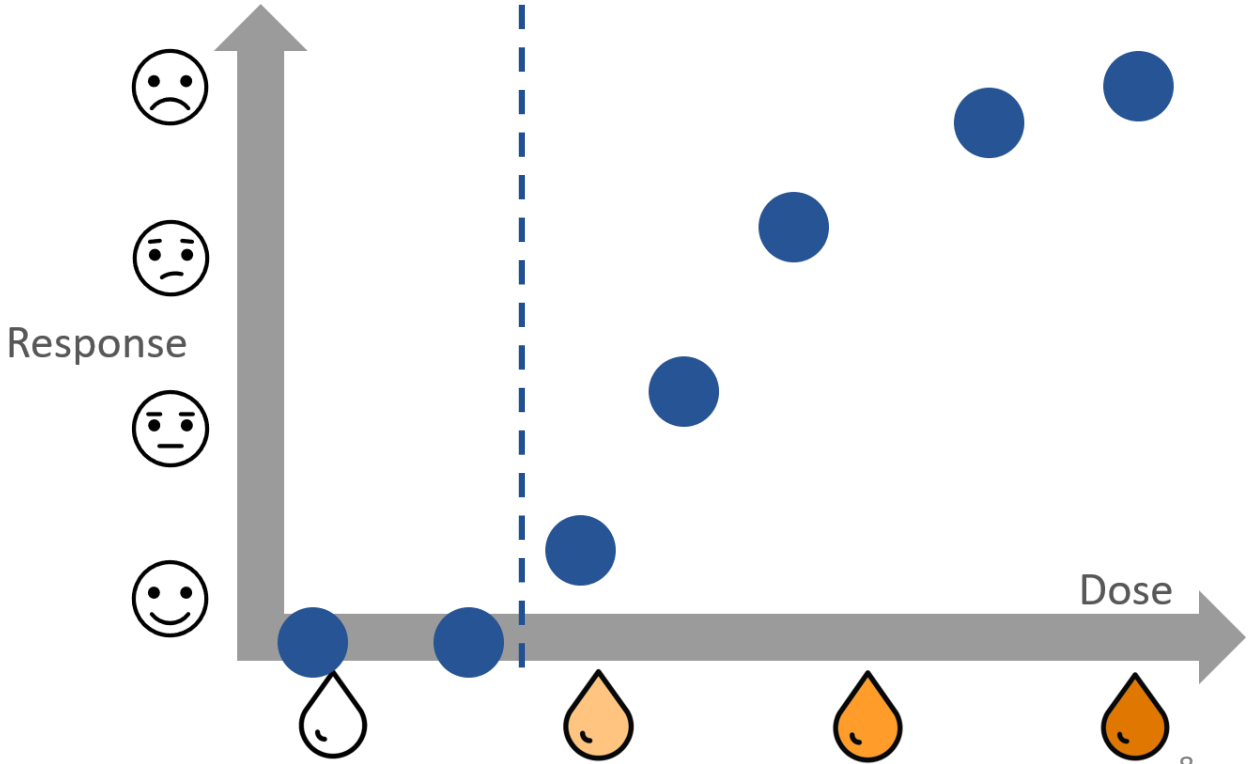
Health Outcomes

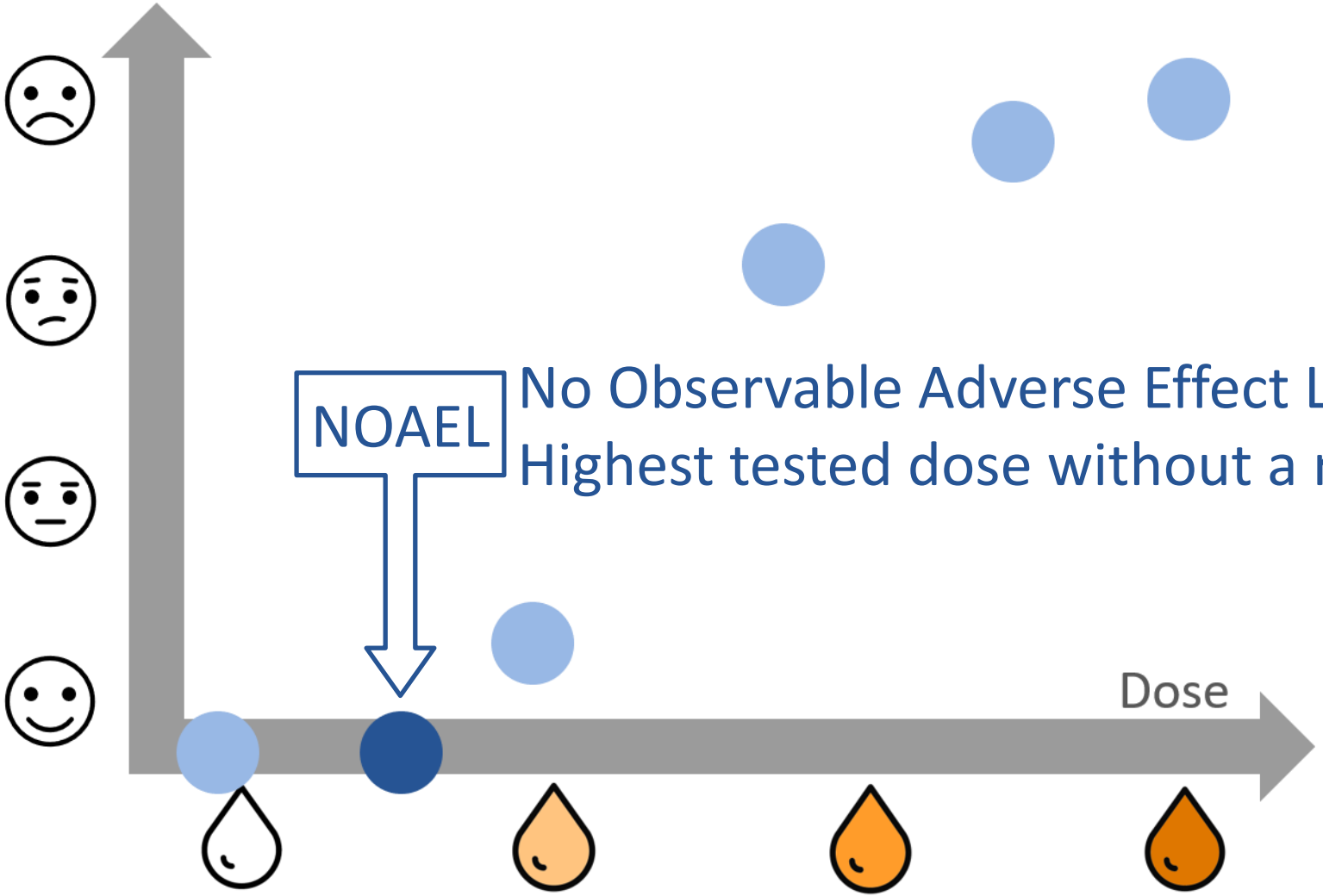
Dose response experiments are used to figure out **how much** of a chemical is needed to cause an effect.

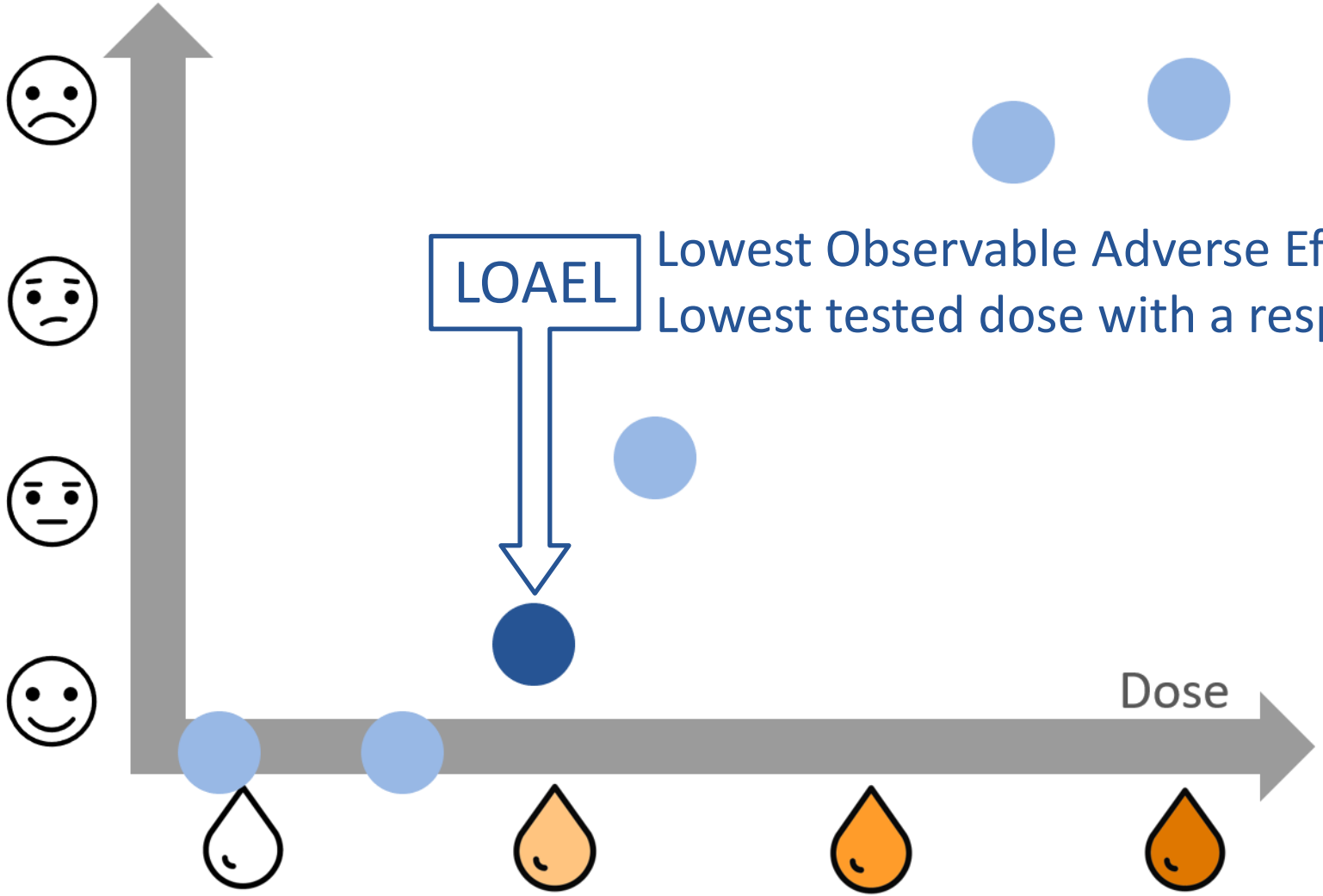

Response
Dose

Most effects have a threshold.

There is some level below which these effects are not expected to occur

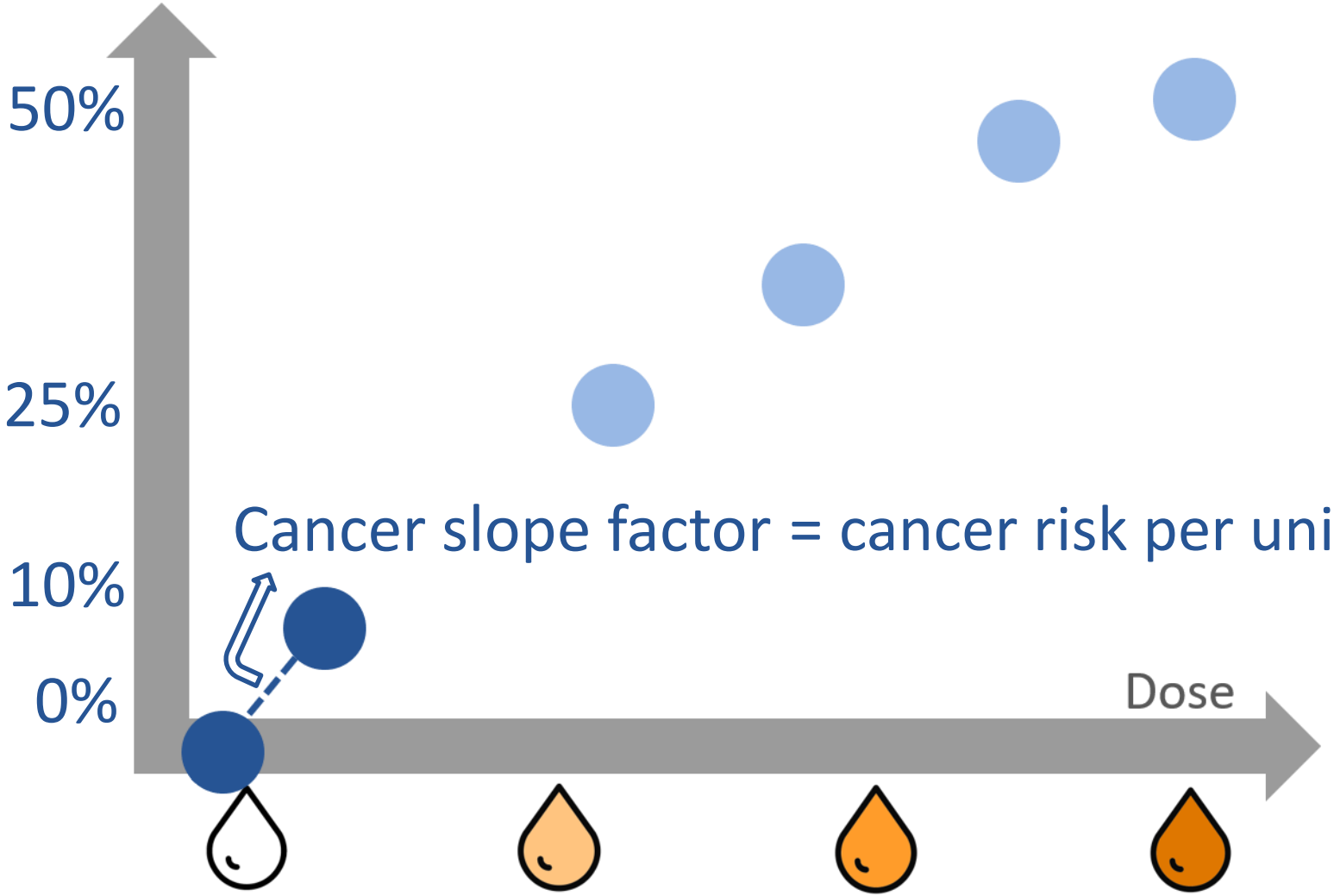



NOAEL
No Observable Adverse Effect Level
Highest tested dose without a response
Dose

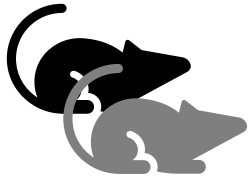

LOAEL
Lowest Observable Adverse Effect Level
Lowest tested dose with a response
Dose

Cancer effects are usually considered to not have a threshold.

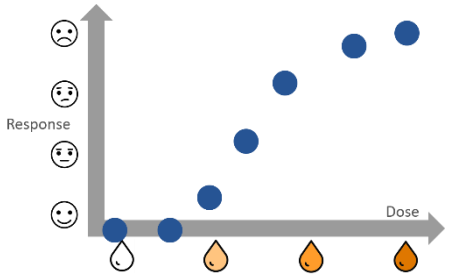
Any level can increase the cancer risk.


50%
25%
10%
0%
Cancer slope factor = cancer risk per unit of dose
Dose

Most human health standards are based on toxicology studies conducted in research animals.



Toxicology studies called dose response experiments are used to figure out **how much** of a chemical is needed to cause an effect.



NOAEL LOAEL Cancer slope factor

Toxicology data are used to set standards that protect health of Wisconsin residents.

Groundwater

Two-thirds of Wisconsin residents use groundwater.

Wisconsin's groundwater standards have 2 parts.

Enforcement Standard

Preventive Action Limit

Groundwater standard process

Identify substances of concern

Develop recommended standards

Promulgate standards

Groundwater standard process

Identify substances of concern

Develop recommended standards

Promulgate standards

The enforcement standard is established from available health information.

Enforcement standards can be based on:

Federal number

State drinking water standard

EPA value

Technical information

Cancer risk

Enforcement standards can be based on:

Federal number

Concentration of a chemical in drinking water that is established by the EPA.

Maximum contaminant level (MCL)

Maximum contaminant level (MCL)

The highest level of a contaminant that is allowed in drinking water.

Maximum contaminant level (MCL) is the highest level of a contaminant that is allowed in drinking water.

Maximum contaminant level goal (MCLG)

The level of a contaminant in drinking water below which there is no known or expected risk to human health.

Maximum contaminant level (MCL)

is set as close to

Maximum contaminant level goal (MCLG)

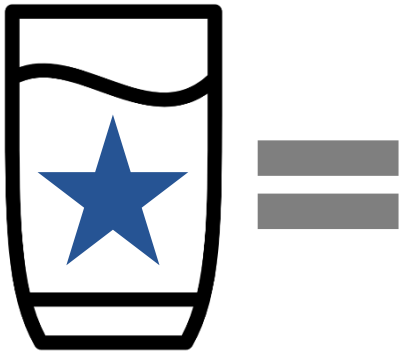
as feasible.

MCLG

= 0

Most carcinogens

All other substances



MCLG

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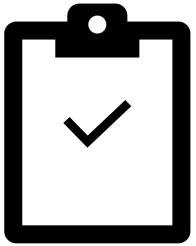
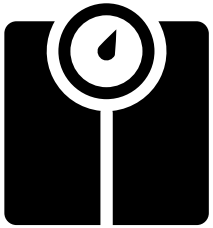


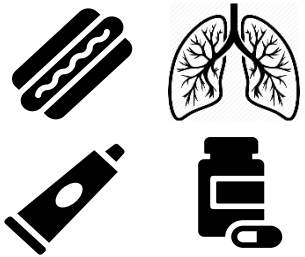
Reference dose

×

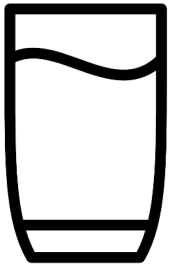


Body weight

×



Relative source contribution



Water consumption

Enforcement standards can be based on:

Federal number

Concentration of a chemical in drinking water that is established by the EPA.

- Maximum contaminant level (MCL)
- Health advisory

Health advisory

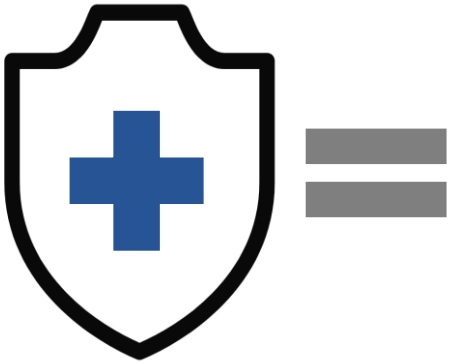
Level at which health effects are not anticipated to occur over a specified duration

Health advisories

1 day

10 day

Lifetime



Health advisory

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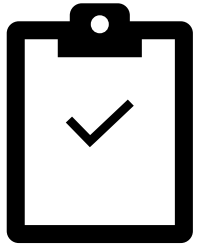

Reference dose

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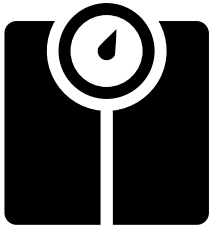

Body weight

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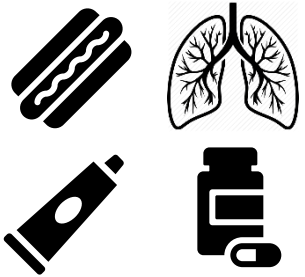
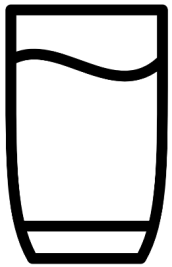


Relative source contribution



Water consumption

Enforcement standards can be based on:

Federal number

Concentration of a chemical in drinking water that is established by the EPA.

- Maximum contaminant level (MCL)
- Health advisory
- Concentration based on cancer risk level

Concentration based on cancer risk level

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Risk level

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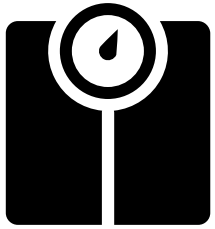
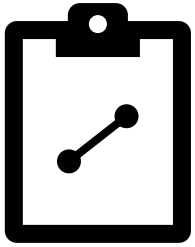


Body weight



Cancer slope factor

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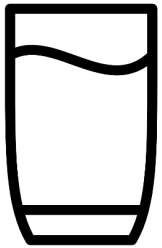


Water consumption

Enforcement standards can be based on:

State drinking water standard

Concentration of a chemical in drinking water that is established by the DNR.

Maximum contaminant level in Wis. Admin Code NR 809

Enforcement standards can be based on:

EPA value

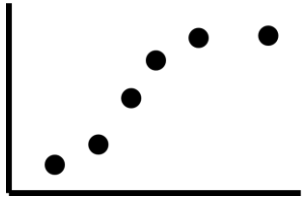
Amount of a chemical a person can be exposed to every day without health effects.

Oral reference dose

Acceptable daily intake (ADI)

Oral reference dose

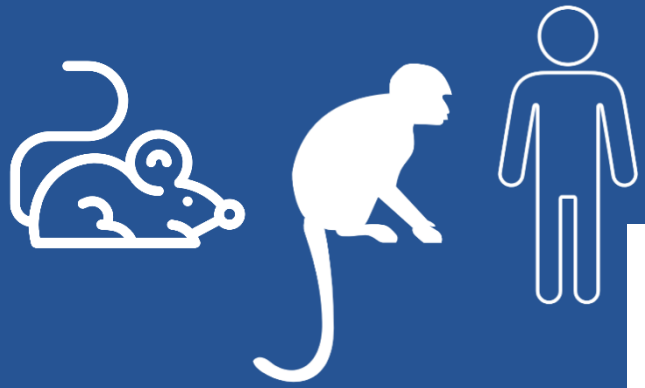
=



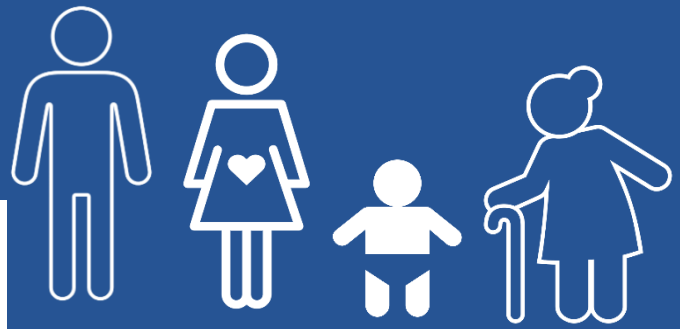
Toxicity value

Uncertainty factor

Species

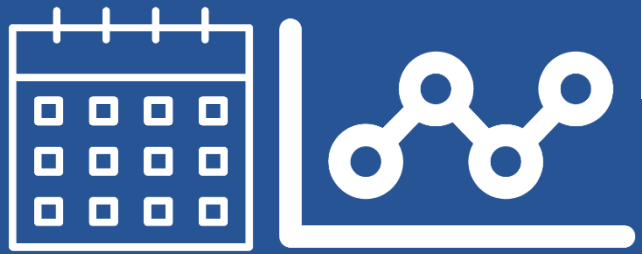


People



Uncertainty factors

Study limitations



Available data

Enforcement standards can be based on:

Technical information

DHS can establish an ADI from available scientific information when:

- There is no federal number or EPA value.
- The information was not considered when the federal number/EPA value was established.

Acceptable daily intake (ADI)

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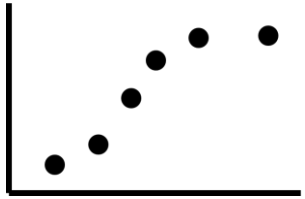

Toxicity value

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Uncertainty factor

Enforcement standards can be based on:

Cancer risk

DHS must ensure the standard does not allow for unacceptable cancer risk.

More than 1 case in 1,000,000 people

When an enforcement standard is based on:

Federal number

State drinking water standard

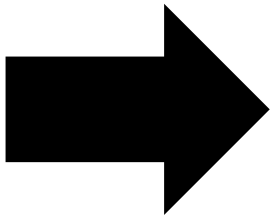
Use the concentration as the standard

When an enforcement standard is based on:

EPA value

Technical information

Cancer risk

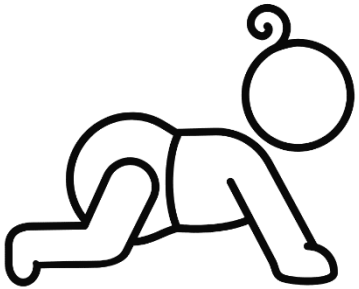


Calculate the appropriate standard

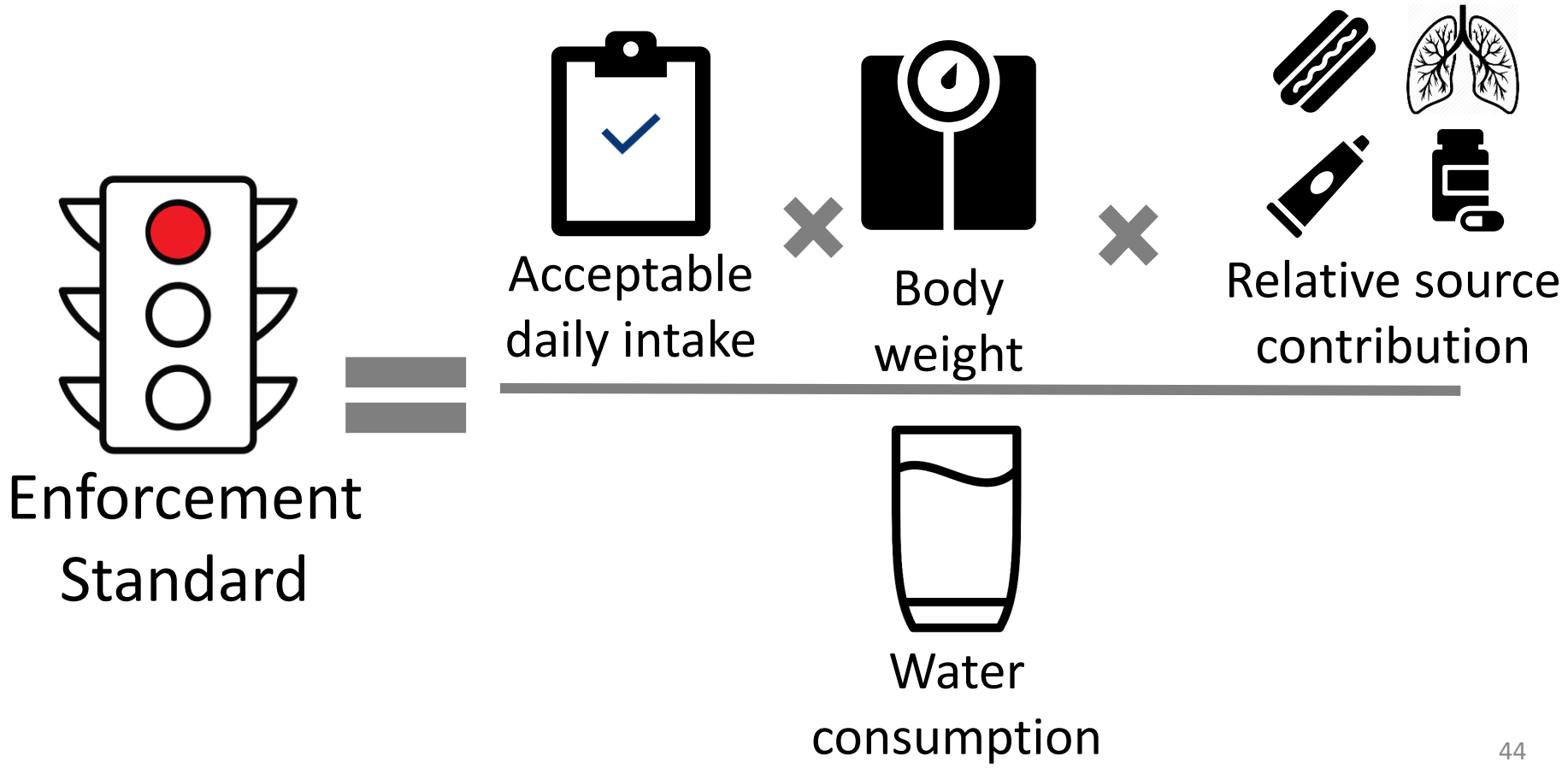
Enforcement standards based on

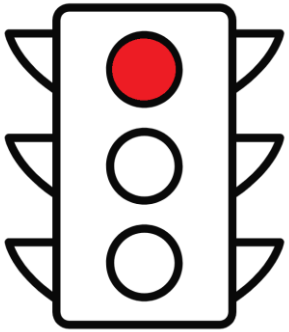
EPA value

Technical information



Set to protect a young child


Enforcement Standard
Acceptable daily intake
Body weight
Relative source contribution
Water consumption



Enforcement Standard

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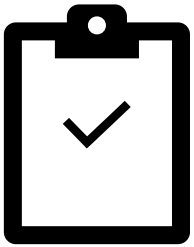

Acceptable daily intake

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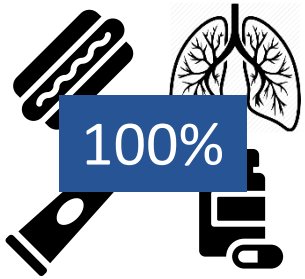
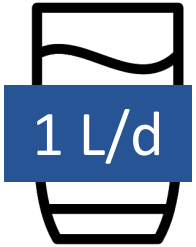
Body weight

×



Relative source contribution

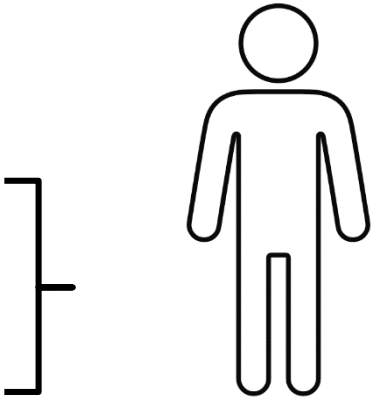


Water consumption

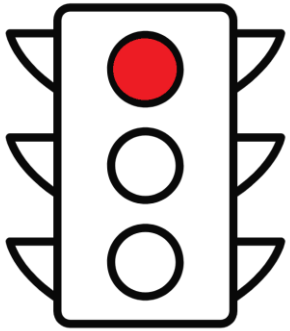
Specified in Statute

Enforcement standards based on

Cancer risk



Set to protect from a lifetime of exposure



Enforcement Standard

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Risk level

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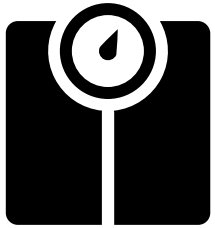
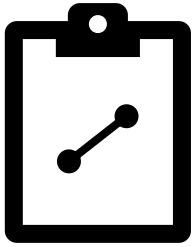


Body weight



Cancer slope factor

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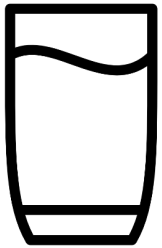
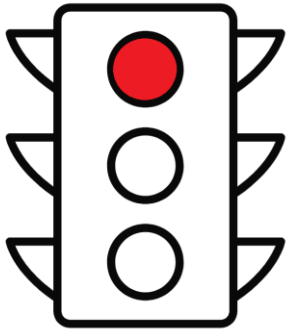


Water consumption



Enforcement Standard

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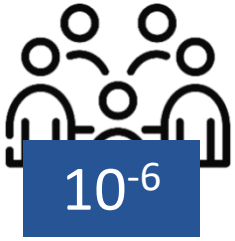
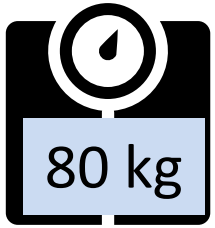
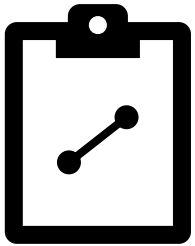


Risk level

×

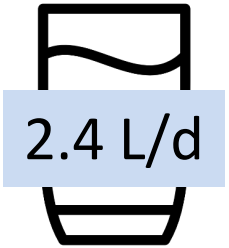


Body weight



Cancer slope factor

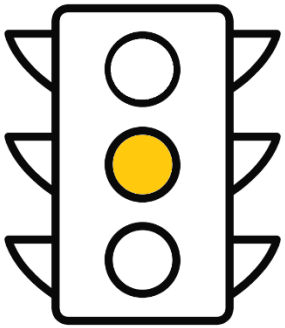
×



Water consumption

Specified in Statute | Recommended by EPA

The preventive action limit is set at a percentage of the enforcement standard.

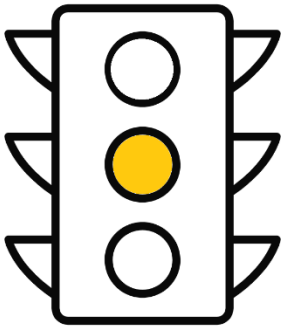


Preventive action limit

= 10%

of the enforcement standard

Substances that cause carcinogenic, mutagenic, teratogenic, or interactive effects



Preventive action limit

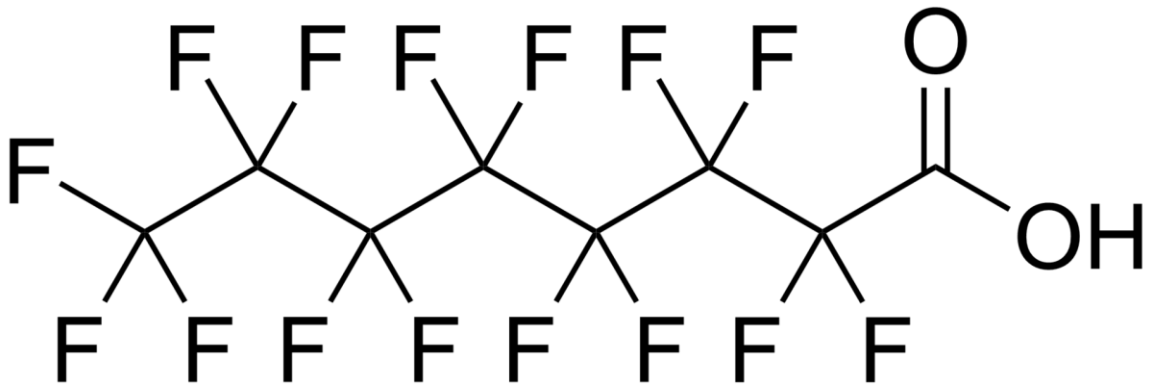
= 20%

of the enforcement standard

All other substances

PFOA

Perfluorooctanoic acid



Available scientific information for PFOA:

Federal number

State drinking water standard

EPA value

Technical information

Cancer risk

Available scientific information for PFOA:

Federal number

Lifetime health advisory

70 ng/L for PFOA and PFOS

Established in 2016

Available scientific information for PFOA:

Federal number

Concentration based on cancer risk

500 ng/L for PFOA

1 in 1,000,000 risk

Established in 2016

Available scientific information for PFOA:

EPA value

Oral reference dose

20 ng/kg-d

Established for use in setting the lifetime health advisory

Available scientific information for PFOA:

Technical information

Intermediate minimum risk level (MRL)

- 3 ng/kg-d
- Proposed by ATSDR in 2018
- Exposure duration of 15 – 365 days

ATSDR = Agency for Toxic Substances and Disease Registry

Available scientific information for PFOA:

Technical information

Critical studies

- Toxicity studies
- Modeling studies

Available scientific information for PFOA:

Cancer risk

Cancer slope factor

$0.07\ (mg/kg\text{-}d)^{-1}$

Established by EPA to set the concentration based on cancer risk

Available scientific information for PFOA:

Federal number

State drinking water standard

EPA value

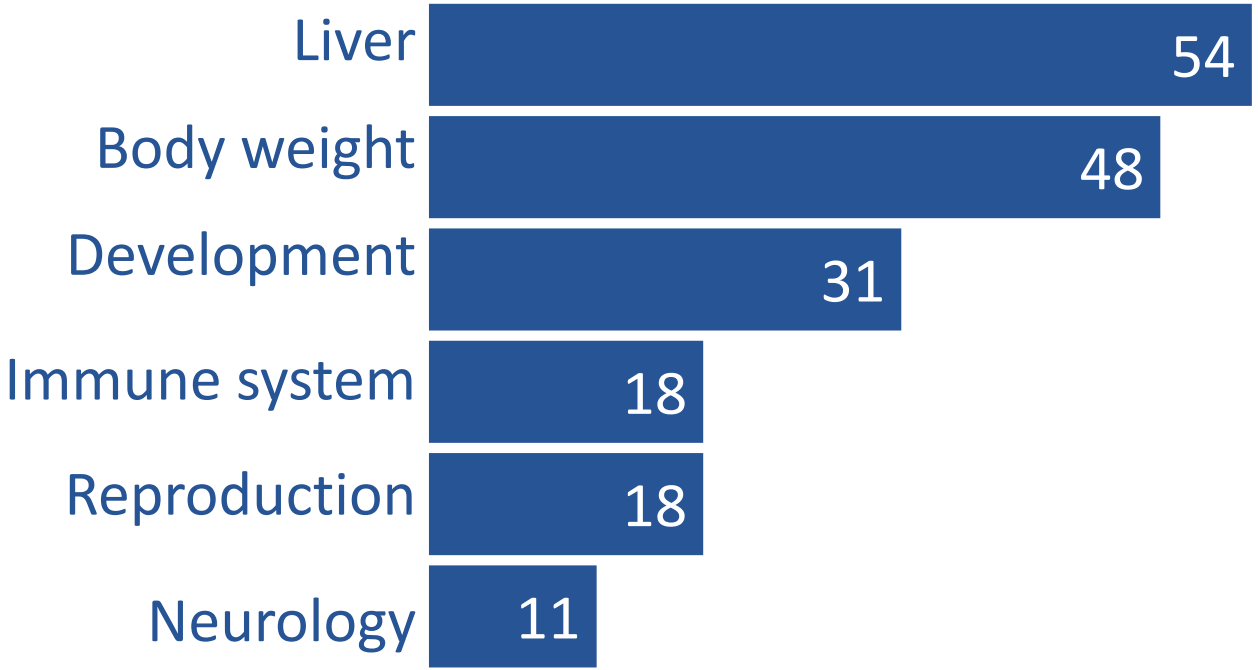
Technical information

Cancer risk

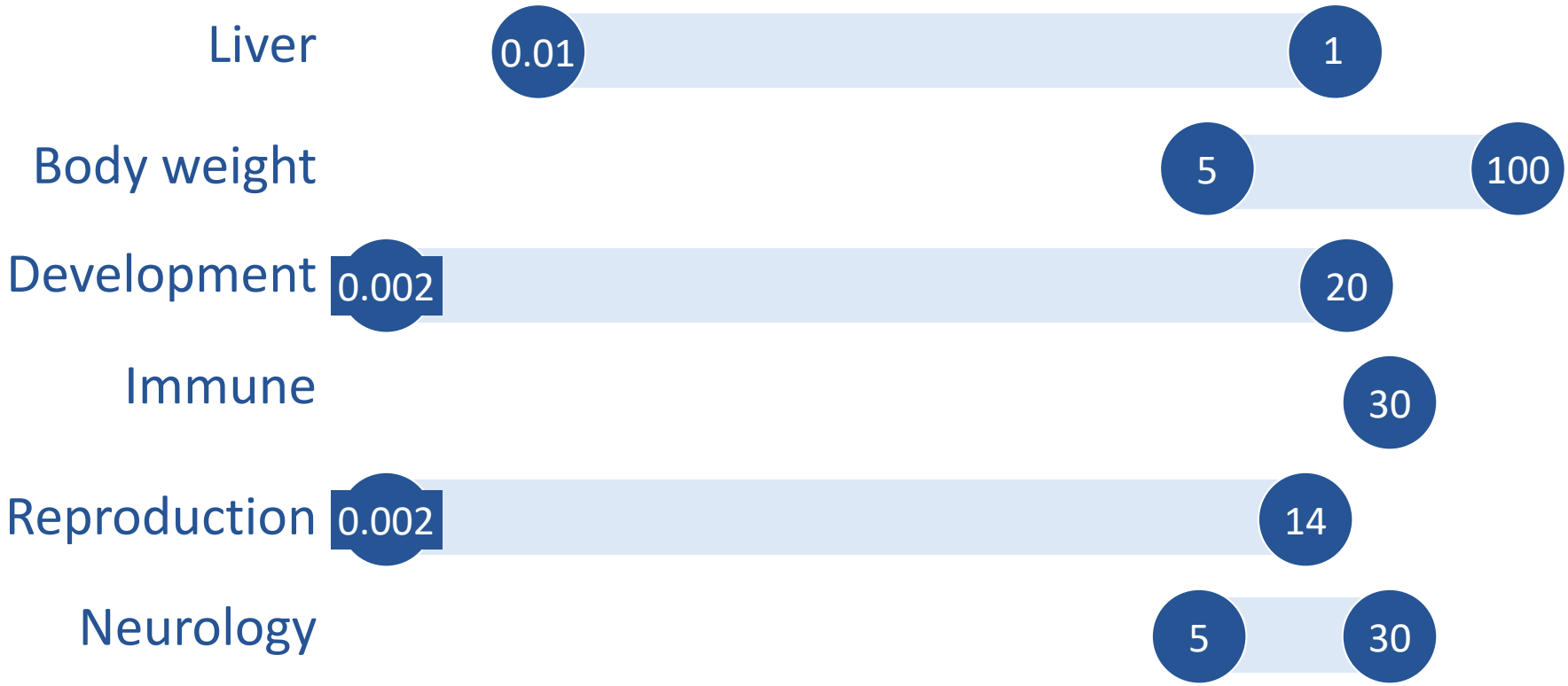
In 2016, EPA established a combined health advisory of 70 ng/L for PFOA and PFOS.

200+ studies evaluating PFOA toxicity in research animals

Most common endpoints:

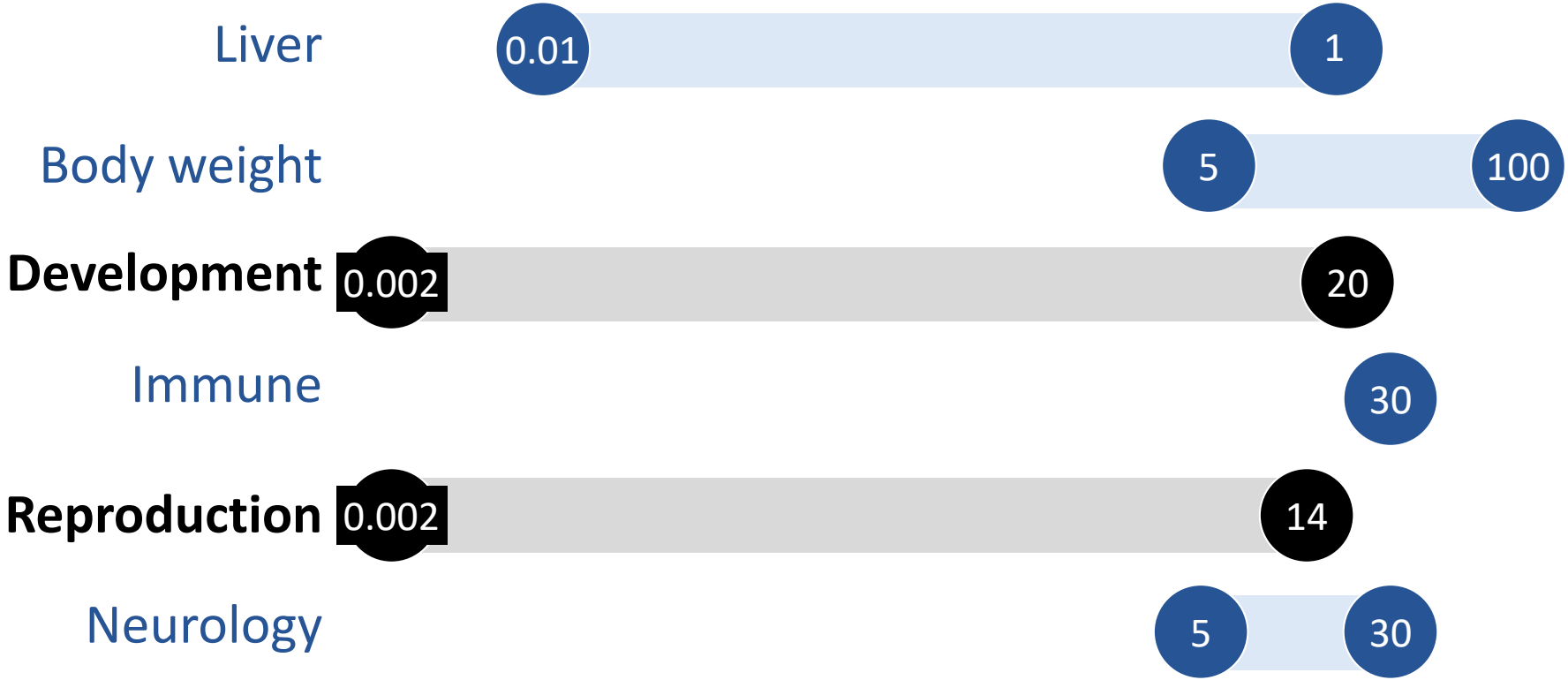


Adapted from Figure 2-1 (ATSDR PFAS Tox Profile)



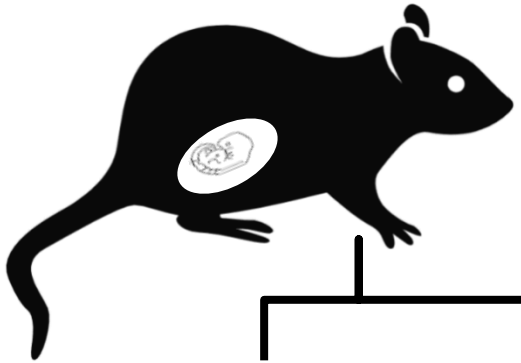
LOAEL ranges from non-acute studies

Development and reproduction are the most sensitive effects.

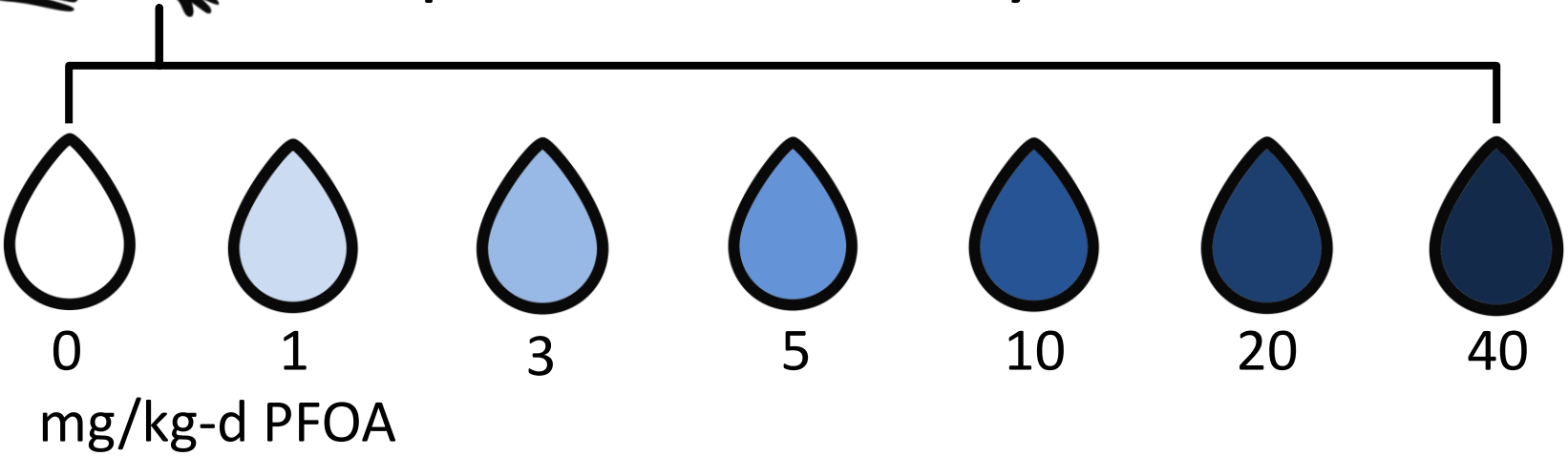


LOAEL ranges from non-acute studies

Babies are most sensitive to the effects of PFOA.



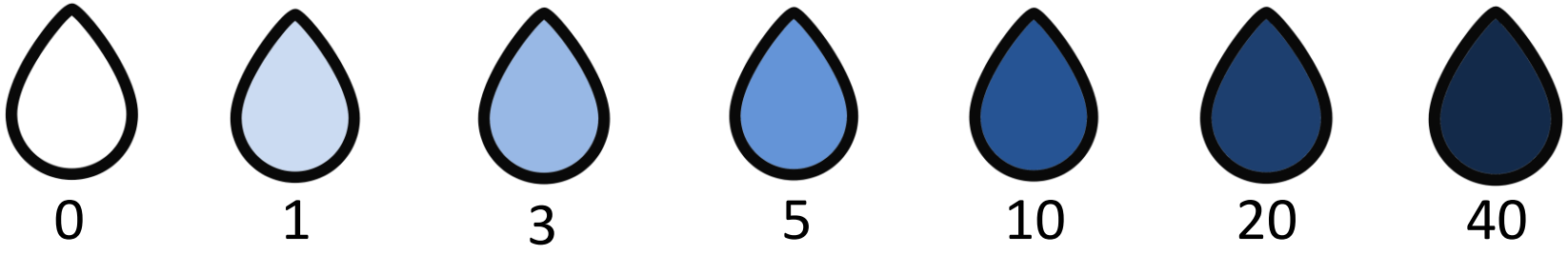
EPA based their advisory on a reproductive study in rats.



Study selected was Lau et al., 2006

Key findings

mg/kg-d PFOA



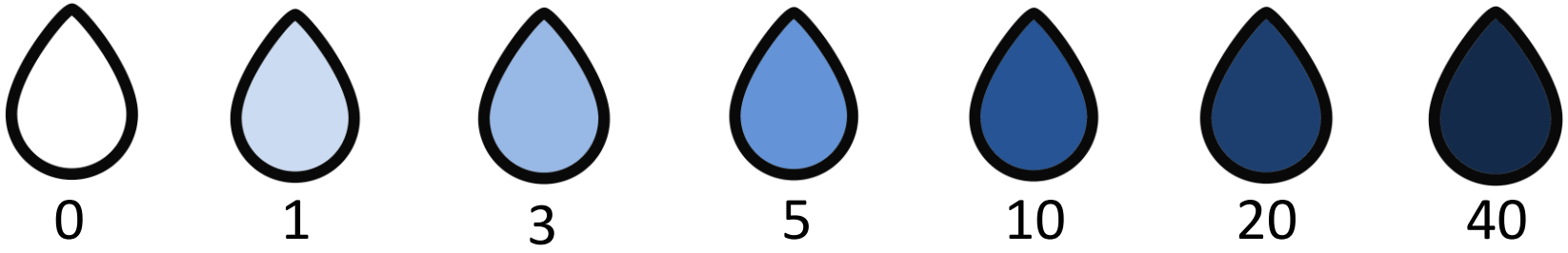
Reproduction

Increased percent of animals with full litter resorption

Summarized from Lau et al., 2006

Key findings

mg/kg-d PFOA



Reproduction

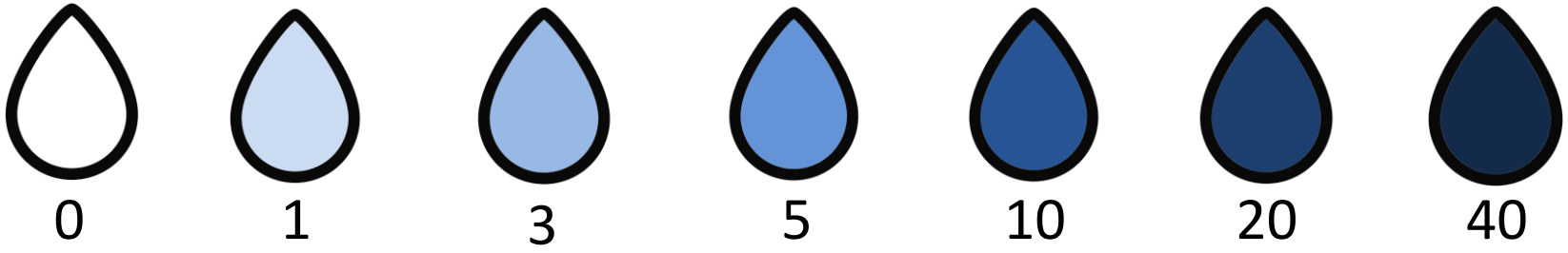
Offspring survival No births

Reduced percent survival based on number of implantations per animal

Summarized from Lau et al., 2006

Key findings

mg/kg-d PFOA



Decreased number of ossification sites in forelimb proximal phalanges

Bone formation

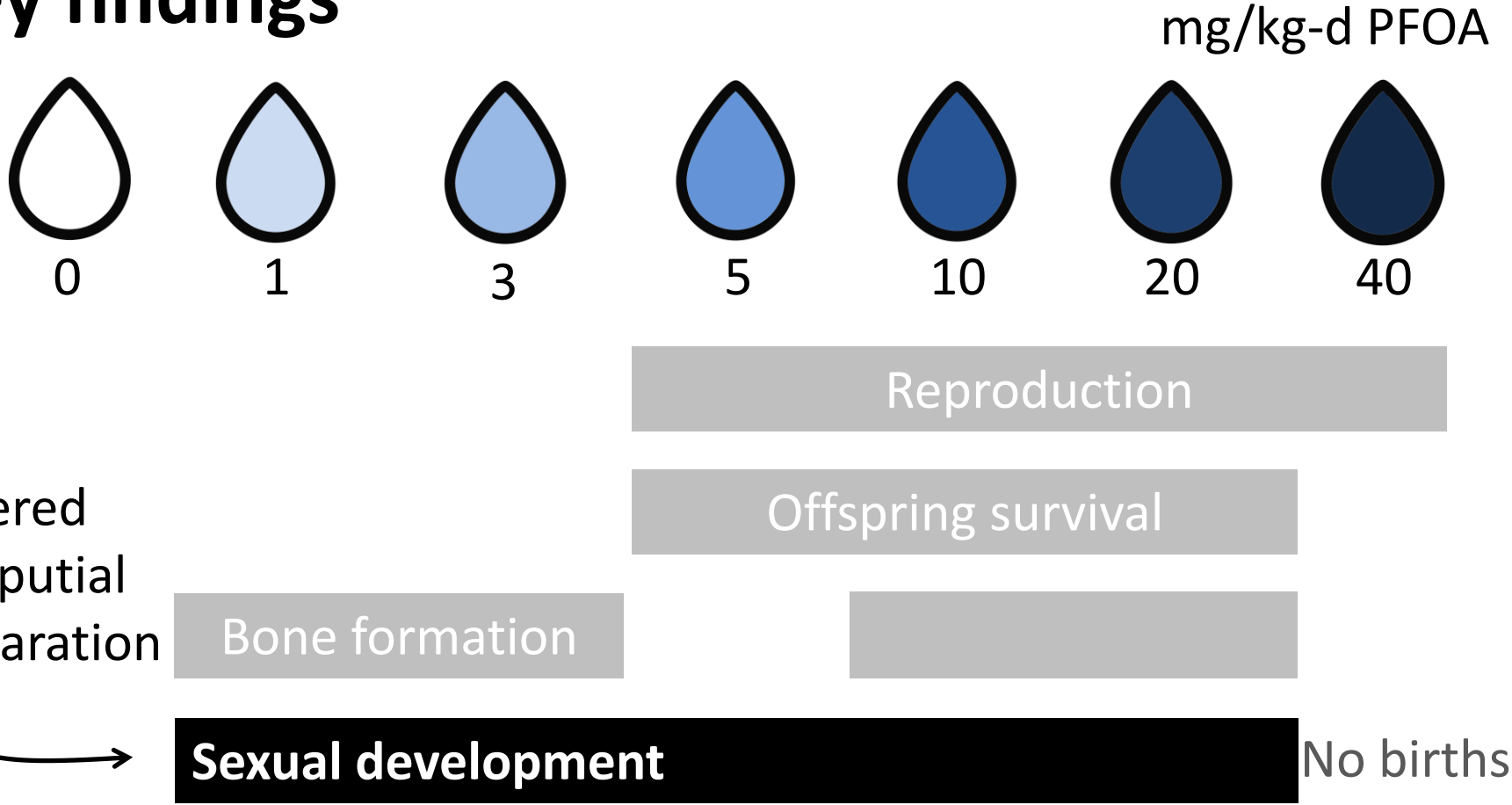
Reproduction

Offspring survival

No births

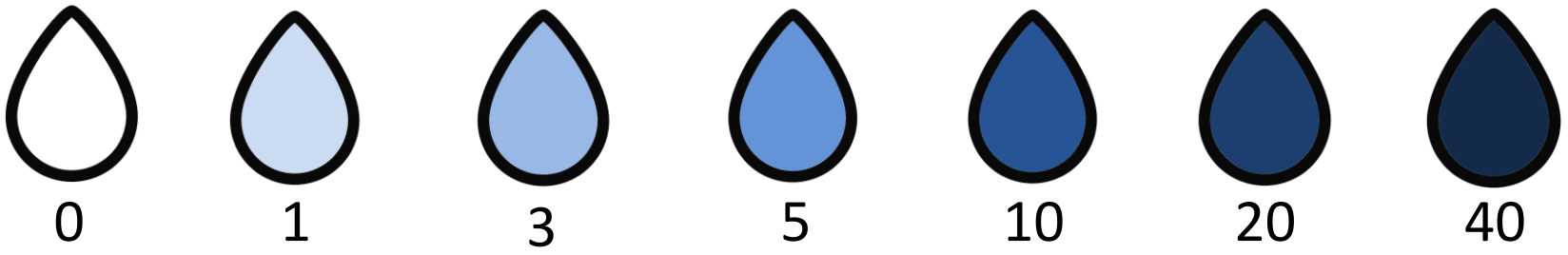
Summarized from Lau et al., 2006

Key findings



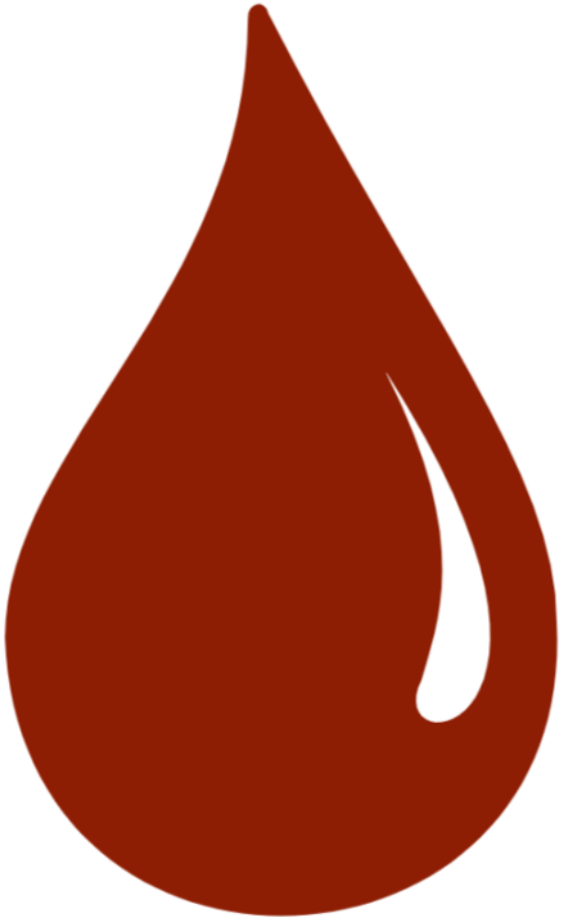
Summarized from Lau et al., 2006

Key findings

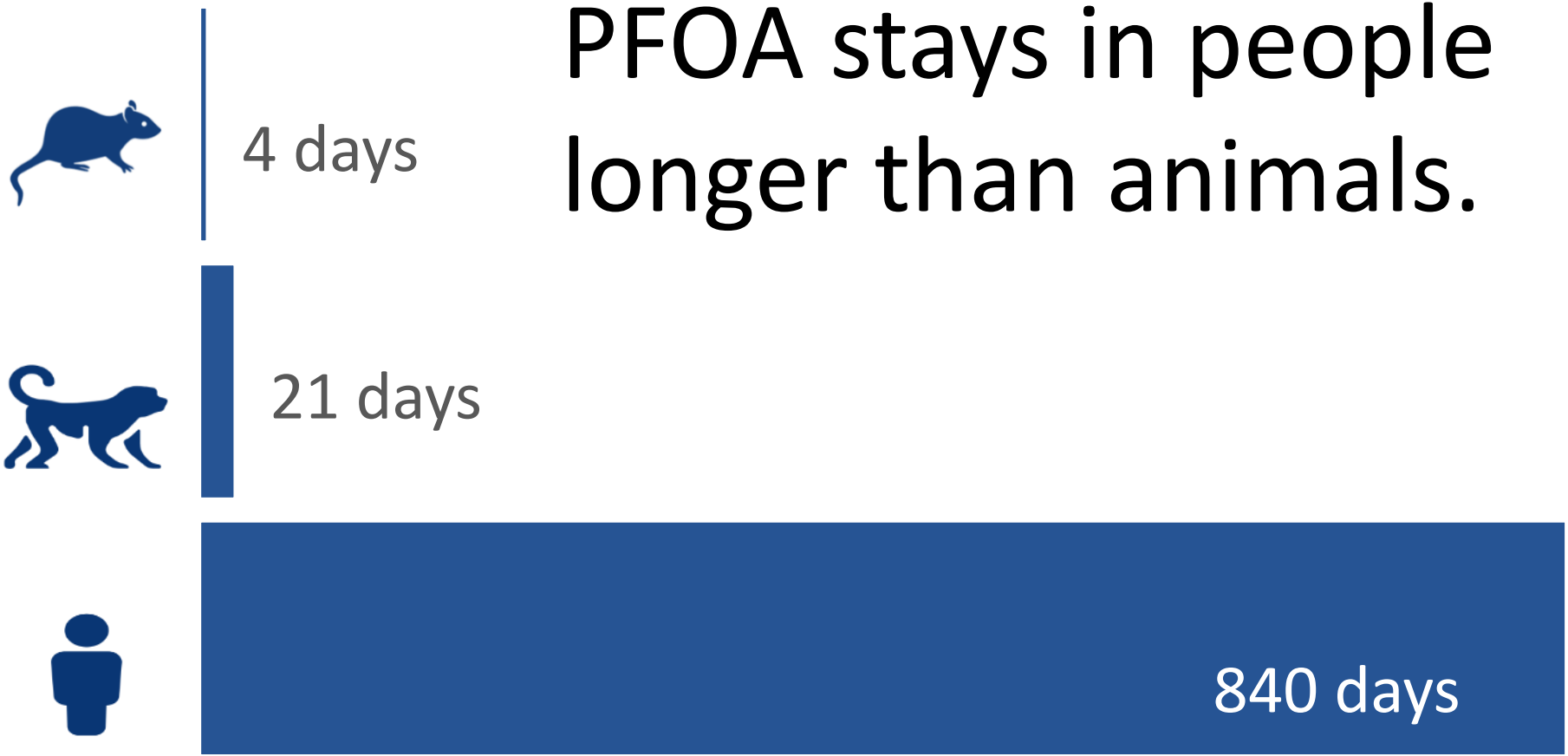


Summarized from Lau et al., 2006

We do not know how much PFAS has to be in our blood to cause health effects.

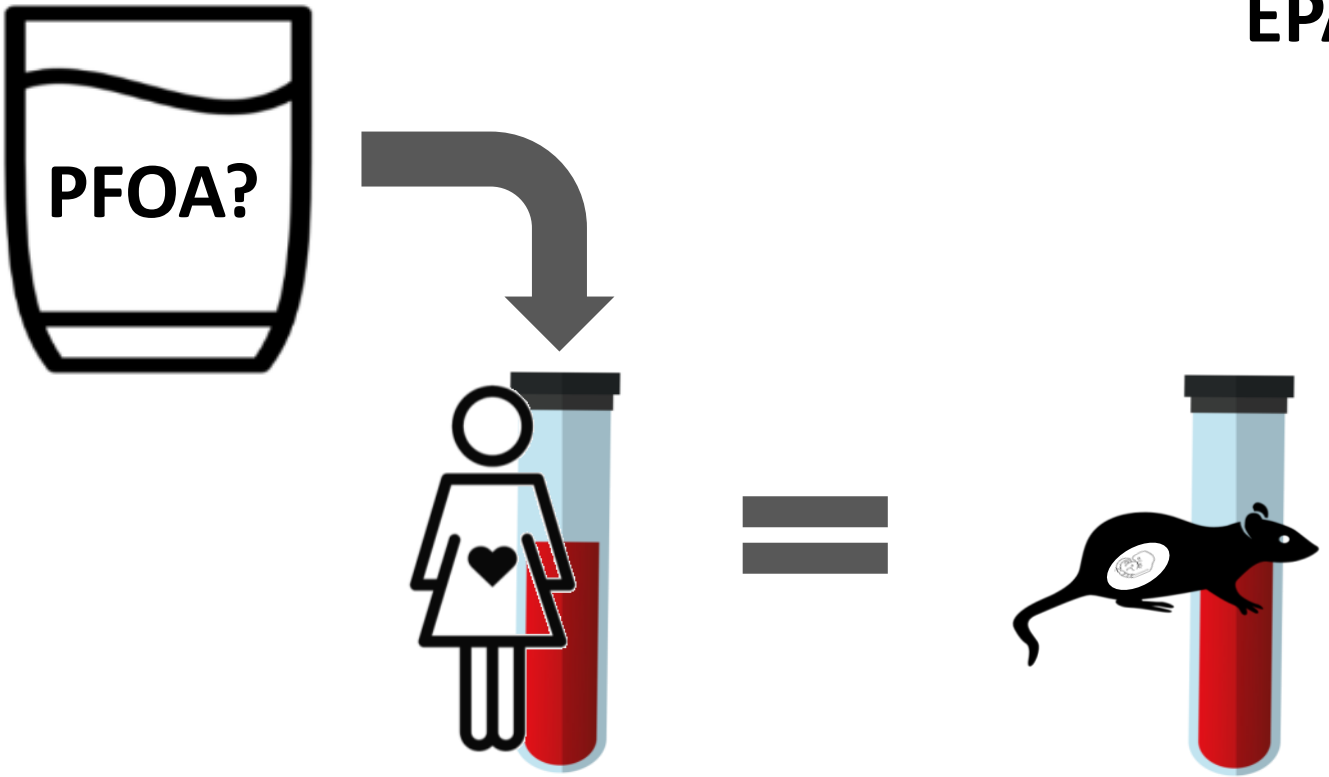


PFOA stays in people longer than animals.



Half-life of PFOA in males

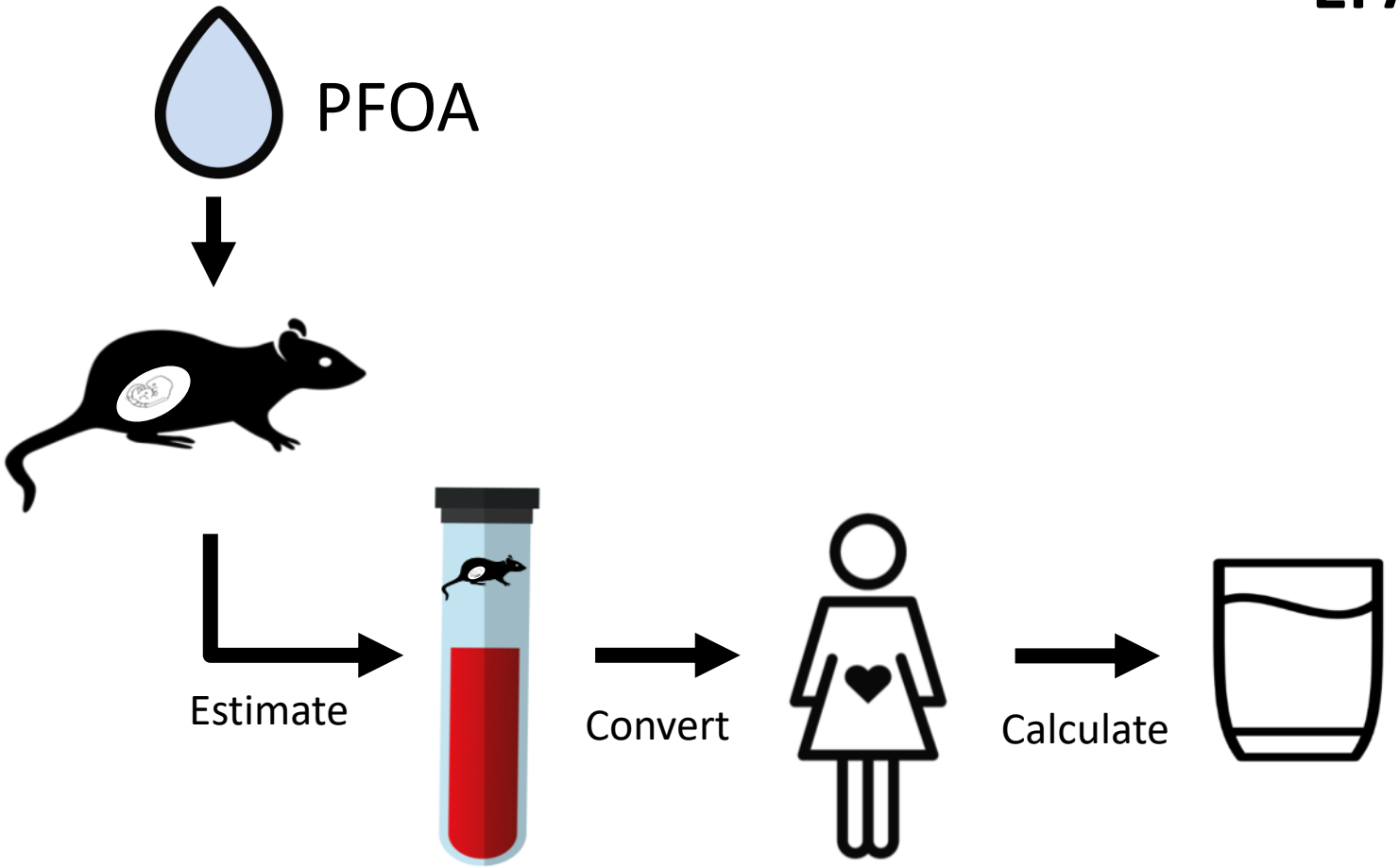
EPA's approach



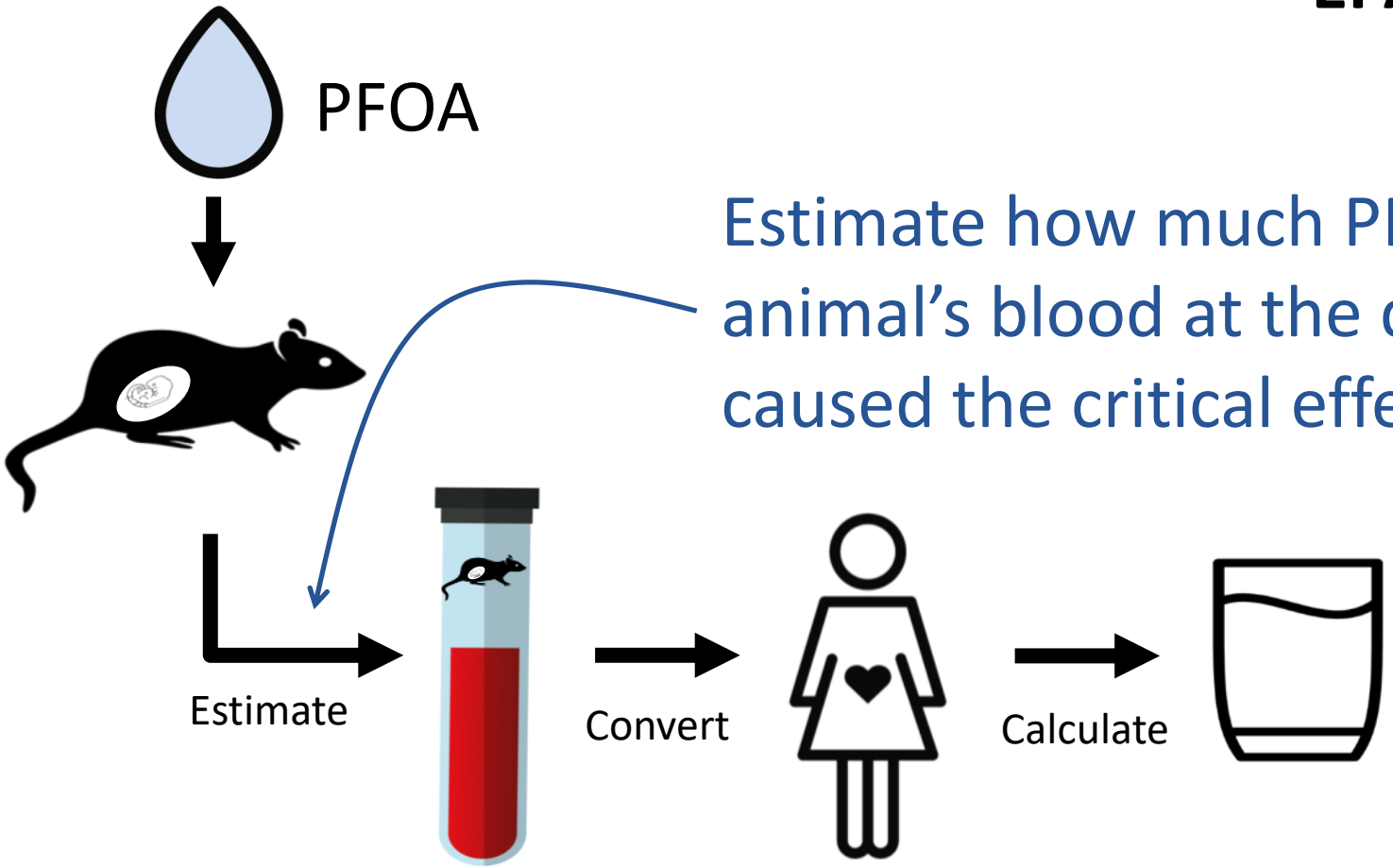
PFOA level in pregnant woman's blood

PFOA level in mother rat's blood at the dose that caused the critical effect in offspring

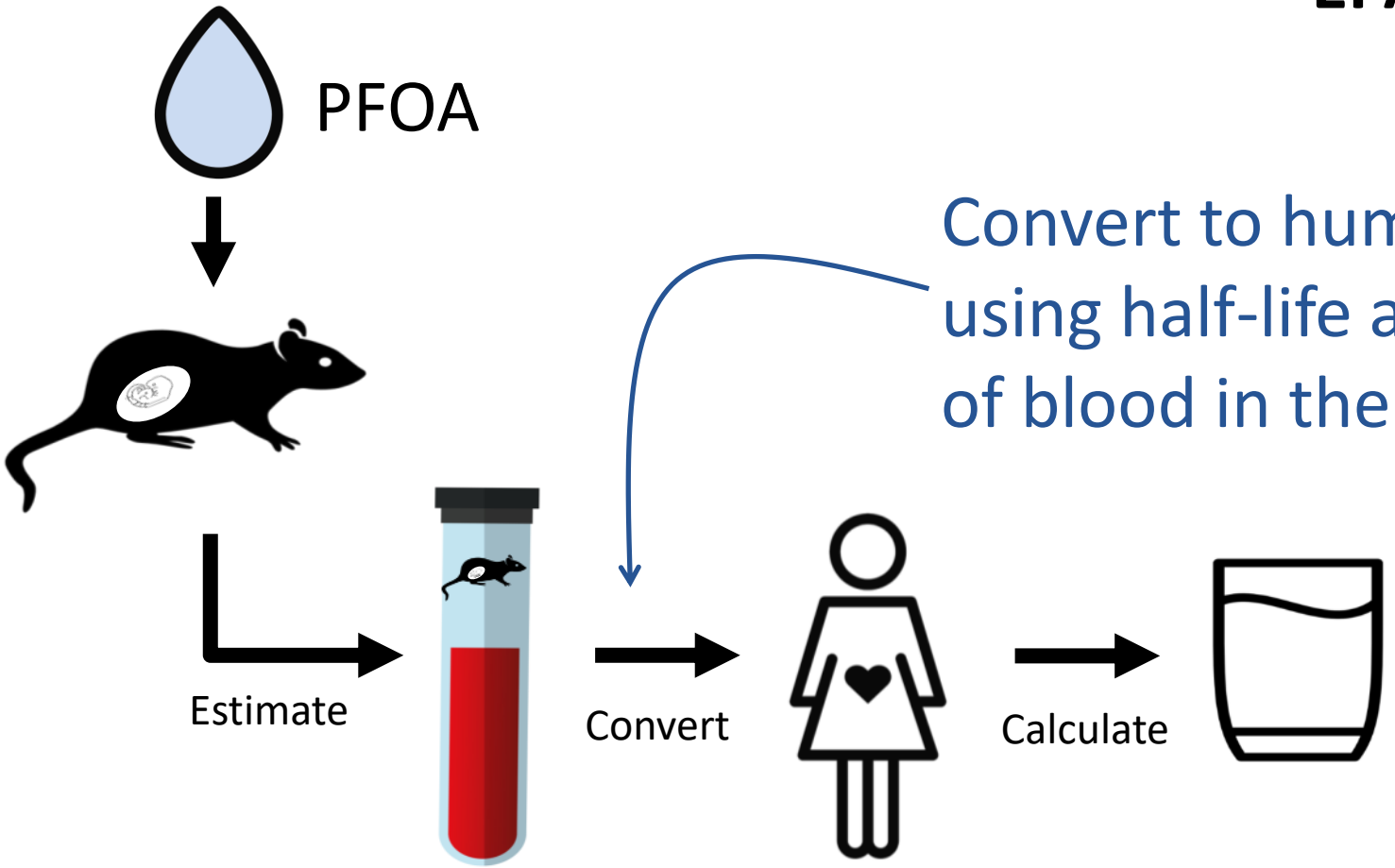
EPA's approach



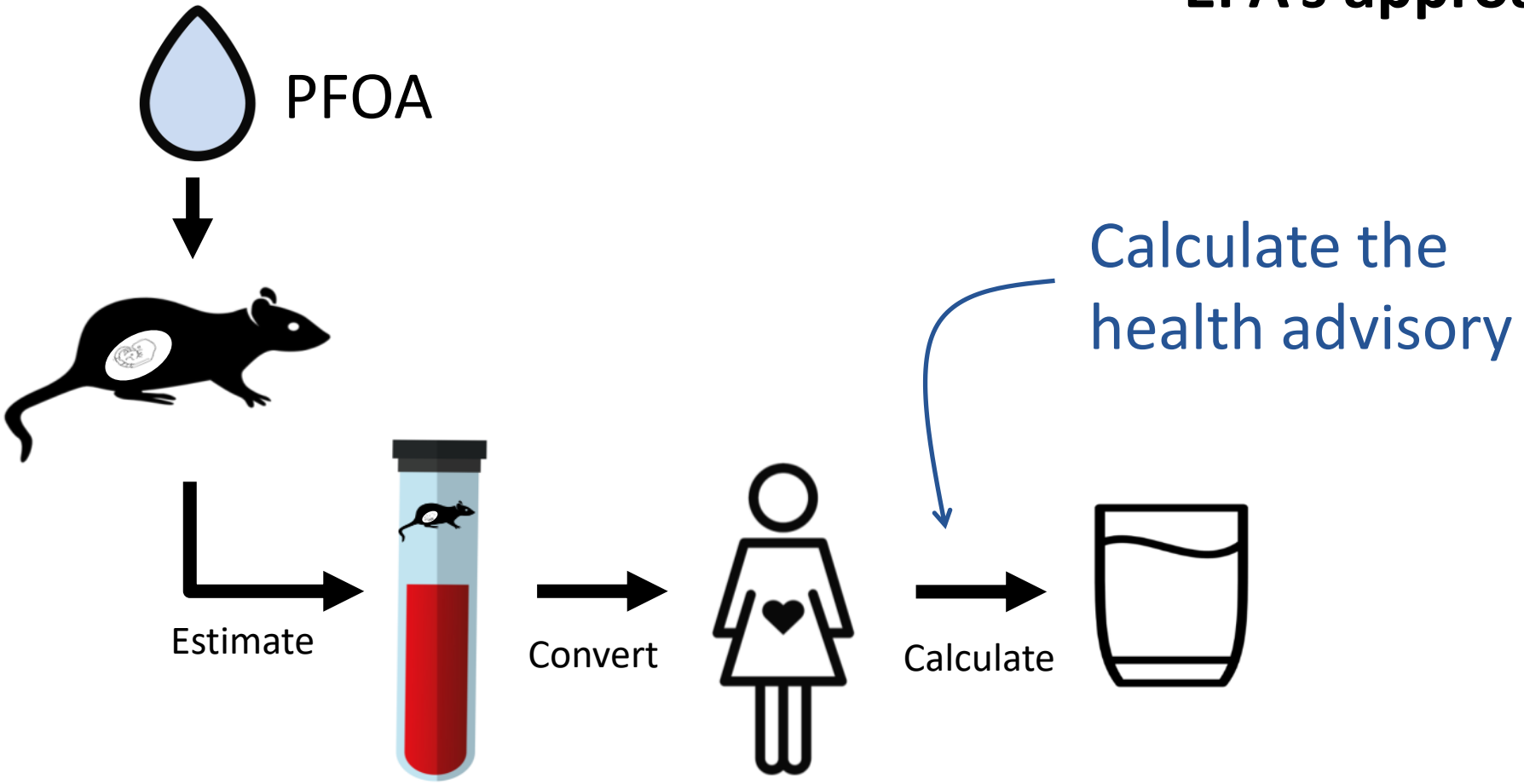
EPA's approach

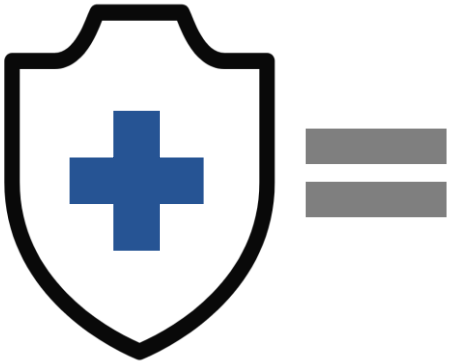


EPA's approach



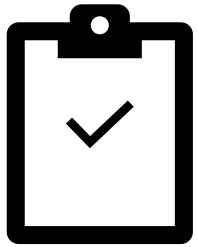
EPA's approach





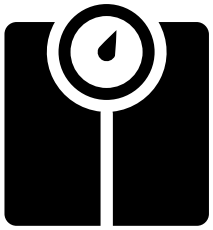
Health advisory

=



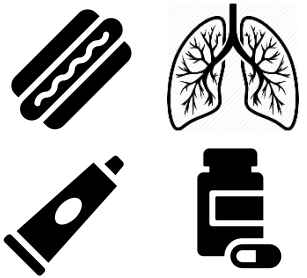
Reference dose

×

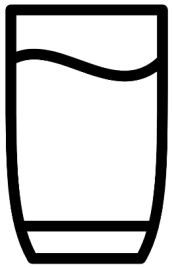


Body weight

×



Relative source contribution



Water consumption

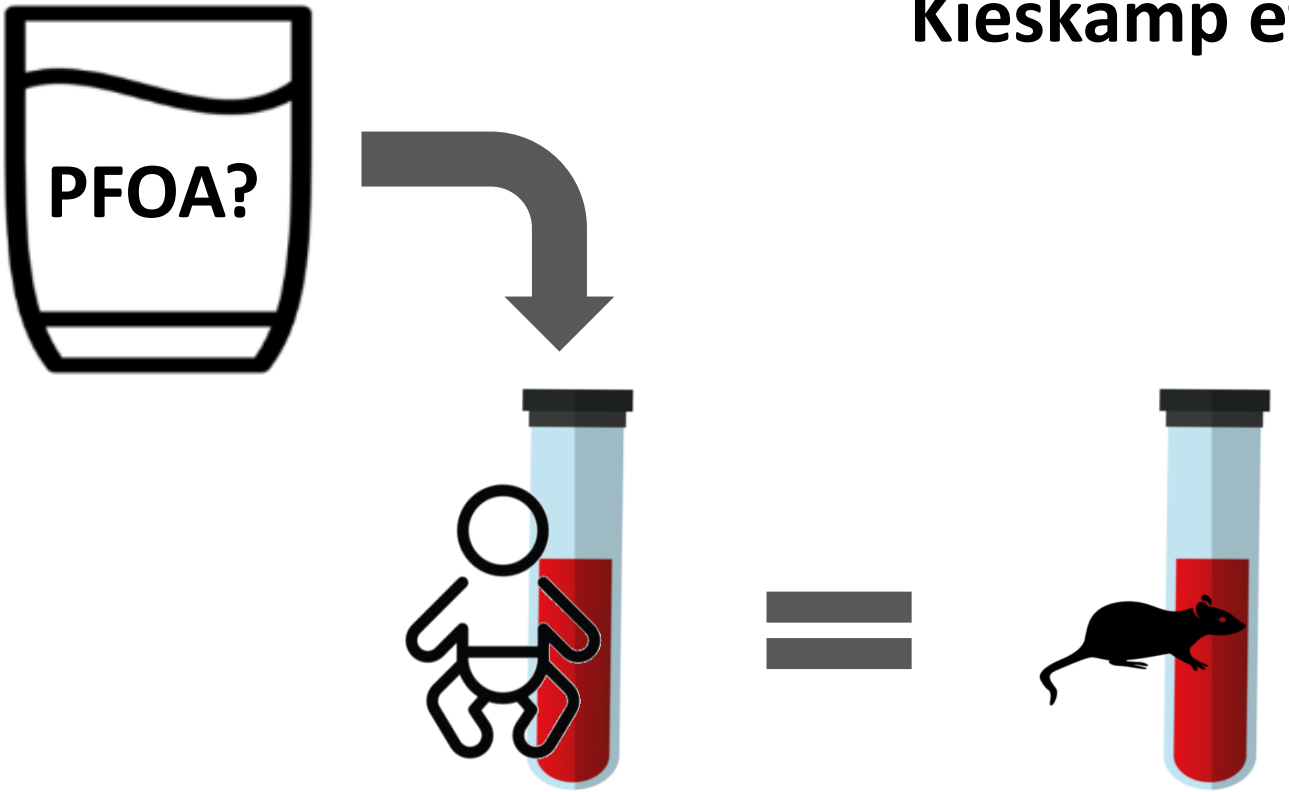
We have learned more about PFOA since 2016.

PFOA can cross the placenta during pregnancy.

PFOA can pass through breastmilk.

How can we best protect unborn and breastfed babies?

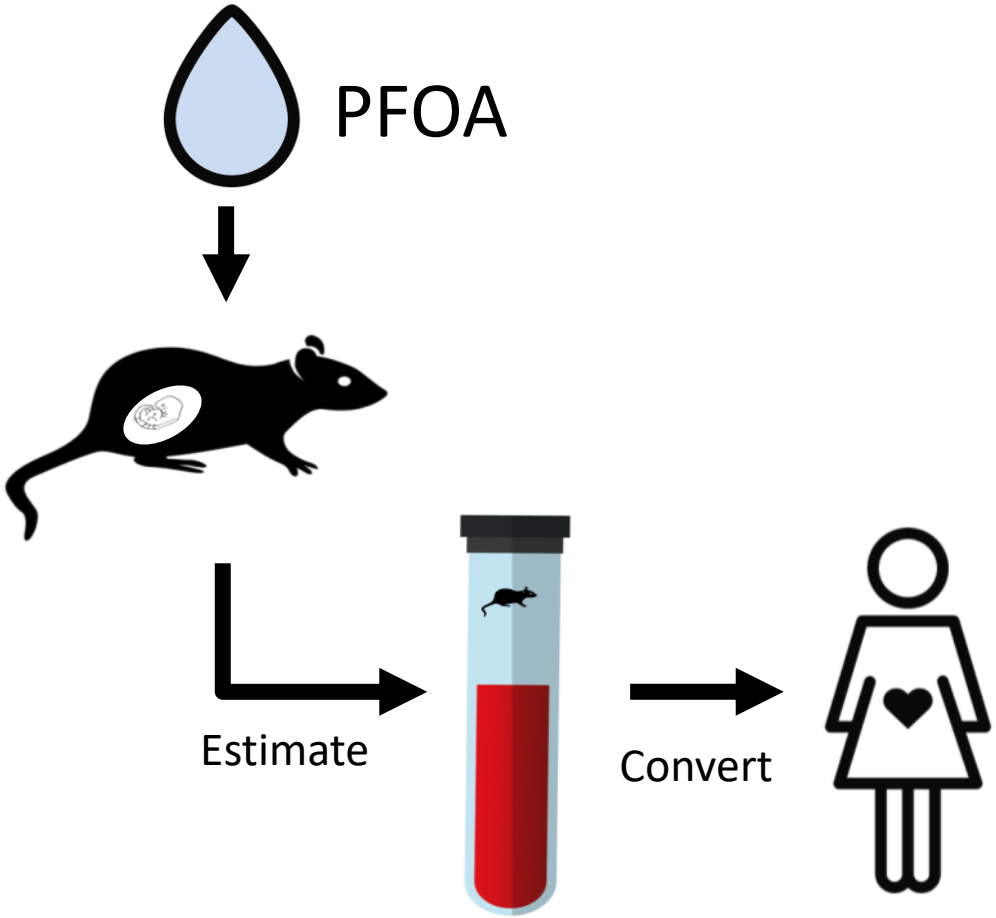
Kieskamp et al. approach



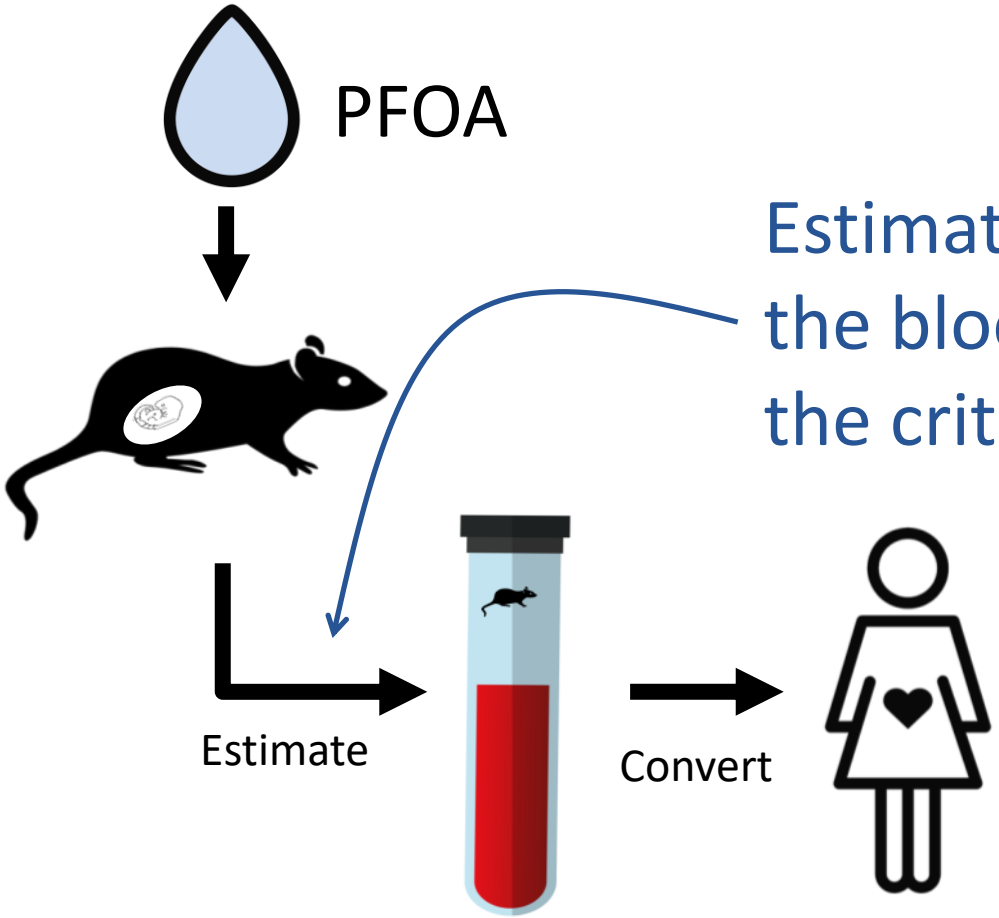
PFOA level in baby's blood

PFOA level in offspring's blood that caused the critical effect

Kieskamp et al. approach

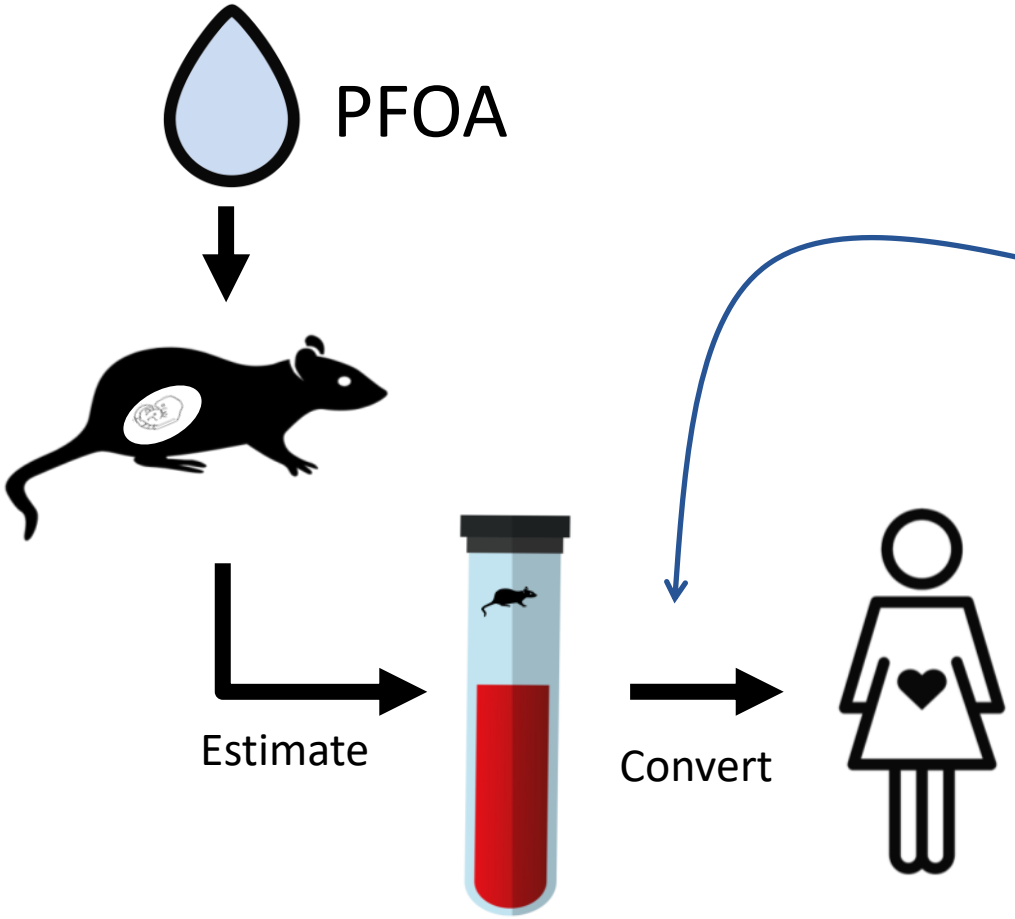


Kieskamp et al. approach



Estimate how much PFOA was in the blood of the offspring that had the critical effect.

Kieskamp et al. approach

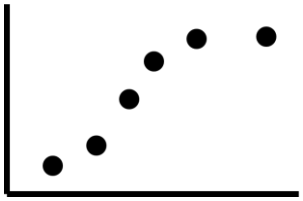


Converted to dose that would cause a baby to have the same level as the offspring – taking into effect half-life and breastfeeding duration

DHS calculations for PFOA:

Acceptable daily intake (ADI)

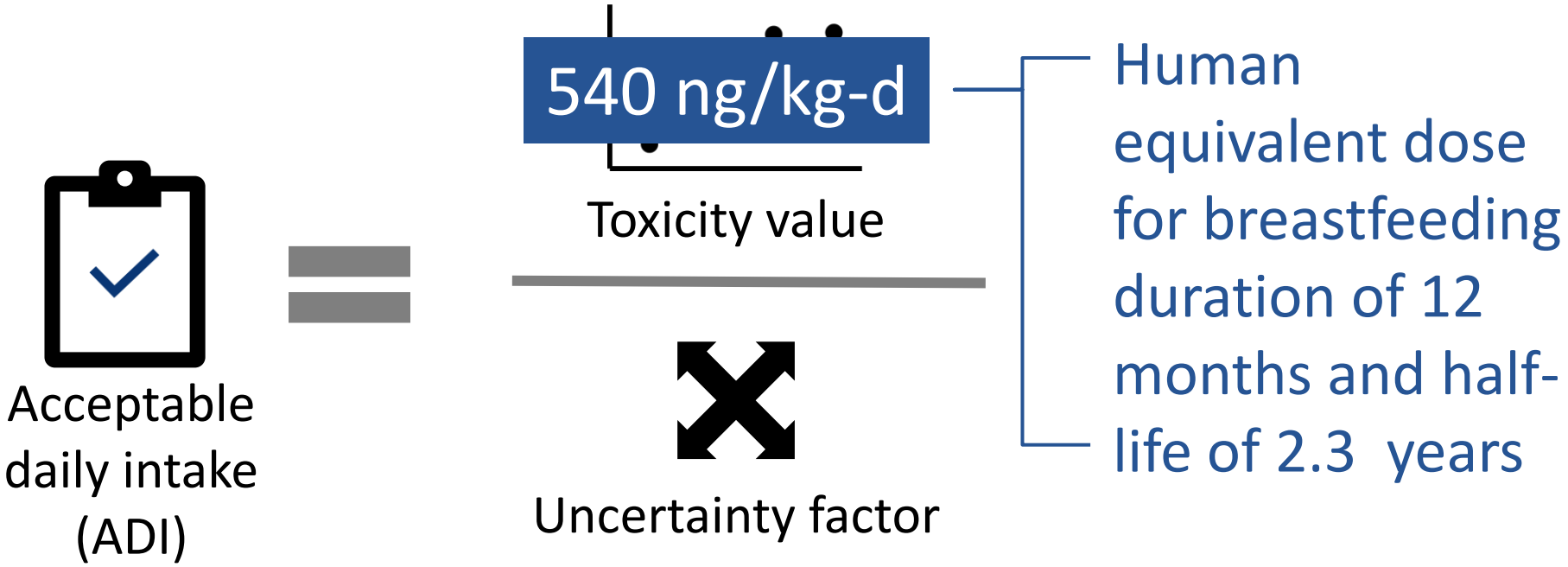
=



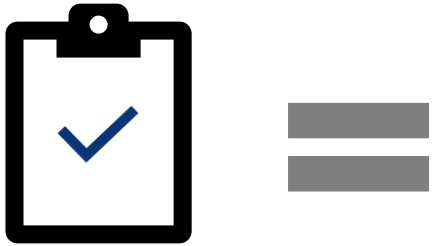
Toxicity value

Uncertainty factor

DHS calculations for PFOA:

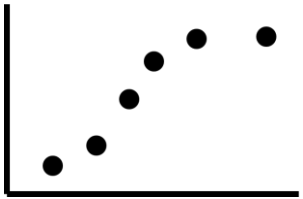


DHS calculations for PFOA:



Acceptable daily intake (ADI)

=



Toxicity value

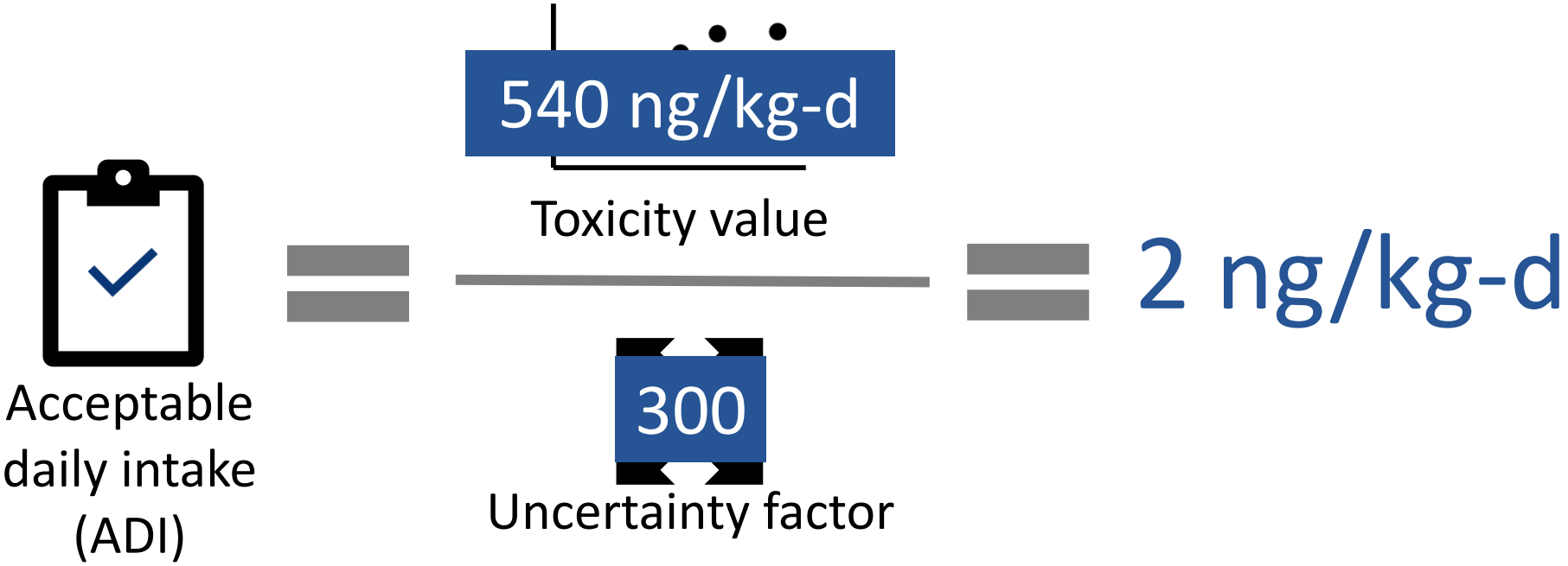
—

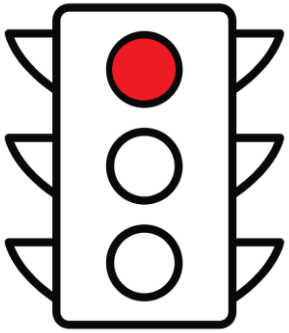
300

Uncertainty factor

Accounts for differences between species, differences among people, and using a LOAEL.

DHS calculations for PFOA:



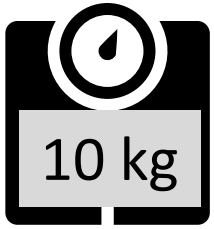


Enforcement Standard

=

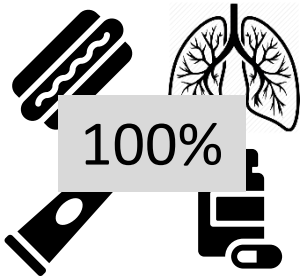
Acceptable daily intake

×

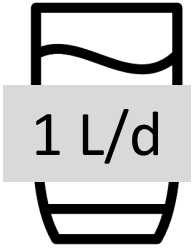


Body weight

×



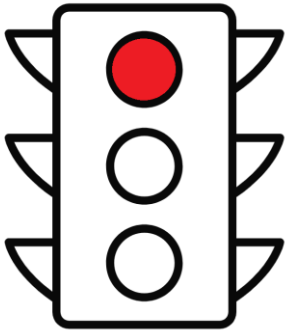
Relative source contribution



Water consumption

Specified in Statute

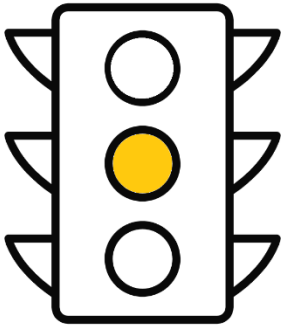
DHS recommendation for PFOA



Enforcement Standard

= 20 ng/L

DHS recommendation for PFOA



Preventive action limit

= 10%

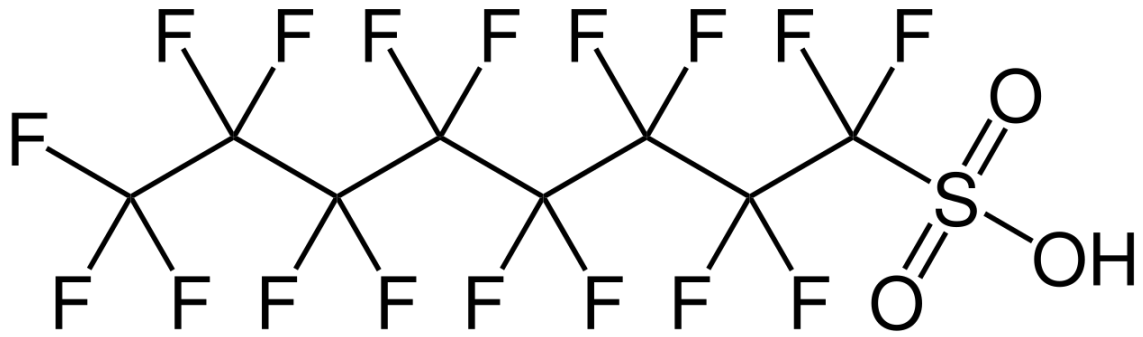
of the enforcement standard

PFOA has been shown to cause carcinogenic, teratogenic, or interactive effects

DHS recommends a combined enforcement standard of 20 ng/L for PFOA and PFOS.

PFOS

Perfluorooctane sulfonate



Available scientific information for PFOS:

Federal number

State drinking water standard

EPA value

Technical information

Cancer risk

Available scientific information for PFOA:

Federal number

Lifetime health advisory

70 ng/L for PFOA and PFOS

Established in 2016

Available scientific information for PFOS:

EPA value

Oral reference dose

20 ng/kg-d

Established for use in setting the lifetime health advisory

160.01(3)

Available scientific information for PFOS:

Technical information

Intermediate minimum risk level (MRL)

2 ng/kg-d

Proposed by ATSDR in 2018

Exposure duration of 15 – 365 days

ATSDR = Agency for Toxic Substances and Disease Registry

Available scientific information for PFOS:

Federal number

State drinking water standard

EPA value

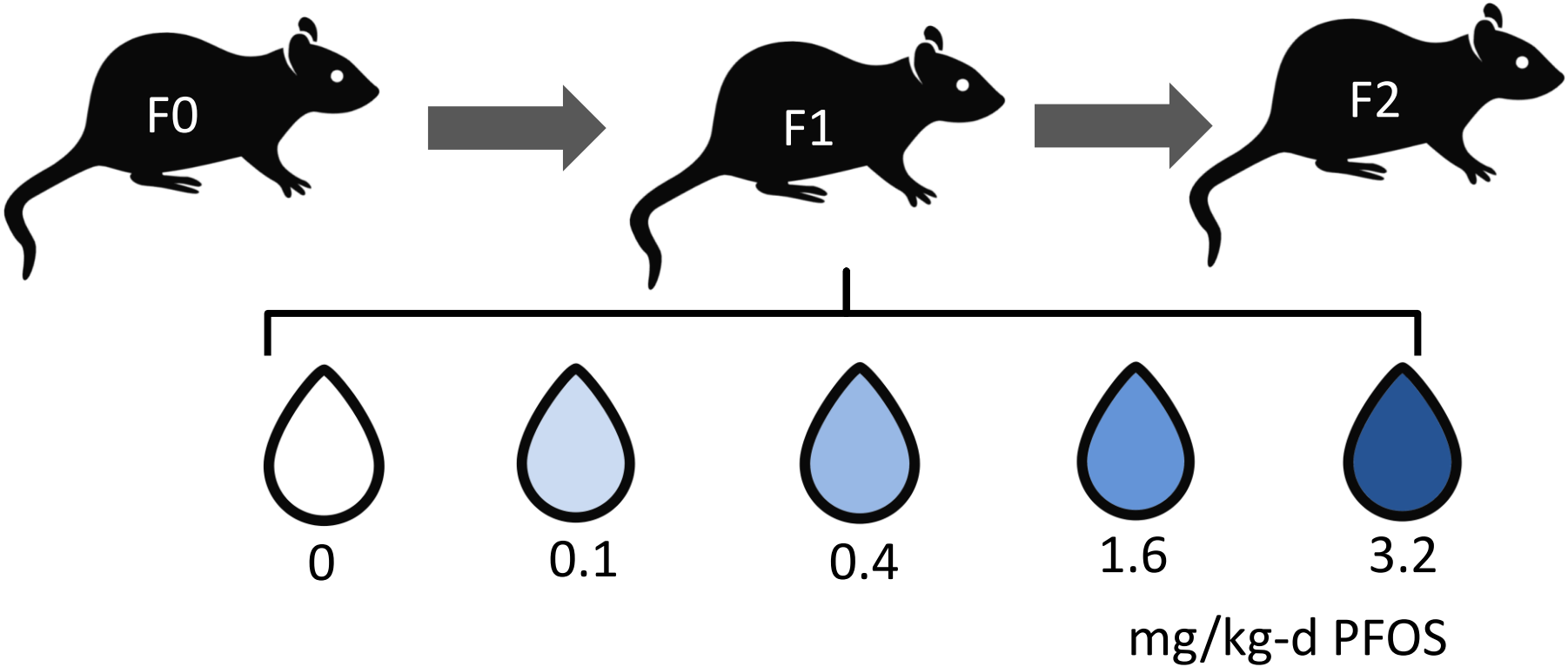
Technical information

Cancer risk

In 2016, EPA established a combined health advisory of 70 ng/L for PFOA and PFOS.

Babies are most sensitive to the effects of PFOS.

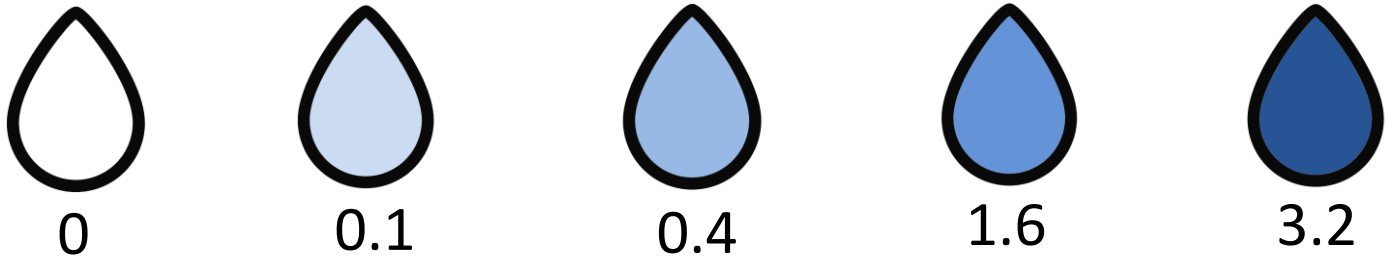
EPA based their advisory on a 2-generation study in rats.



Study selected was Luekber et al., 2005b

Key findings

mg/kg-d PFOS



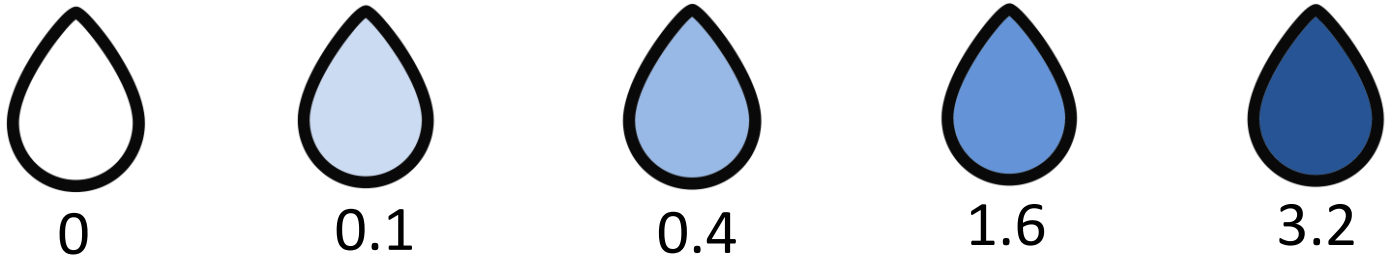
Body weight (F0)

Reduced body weight in males and females at various timepoints during exposure - corresponding with reduced food consumption

Summarized from Luebker et al., 2005b

Key findings

mg/kg-d PFOS



Body weight (F0)

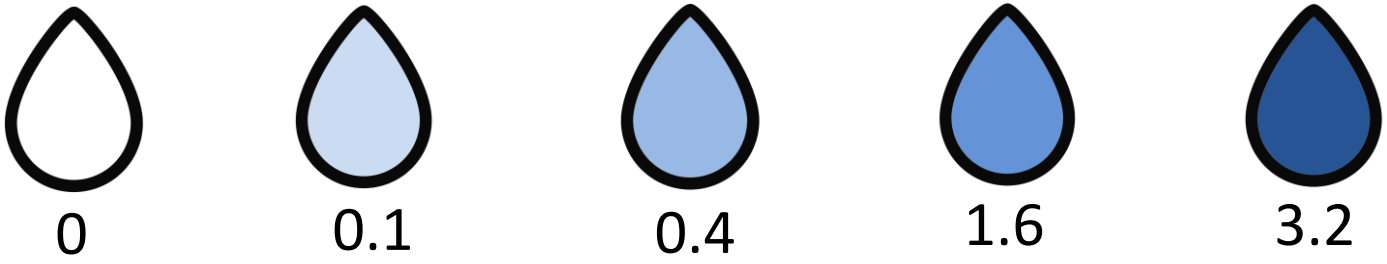
Survival (F1)

Increased in number of pups found dead and decreased viability and lactation indices.

Summarized from Luebker et al., 2005b

Key findings

mg/kg-d PFOS



Body weight (F0)

Survival (F1)

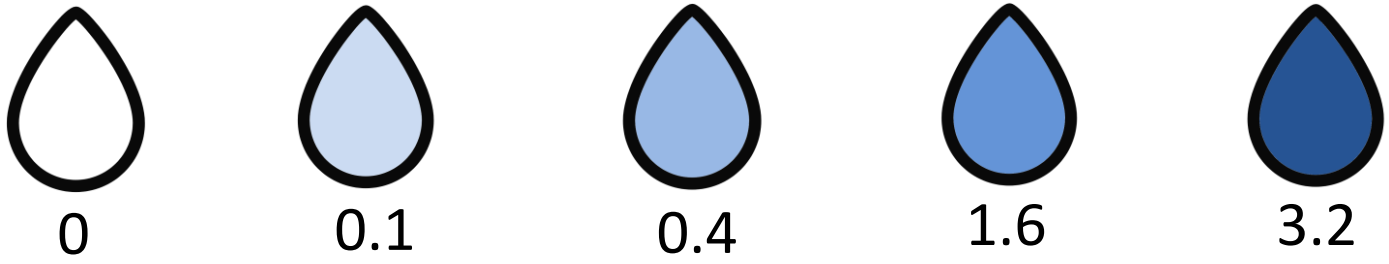
Decreased weight per litter and reduced weight change per litter

Body weight (F1)

Summarized from Luebker et al., 2005b

Key findings

mg/kg-d PFOS



Body weight (F0)

Survival (F1)

Body weight (F1)

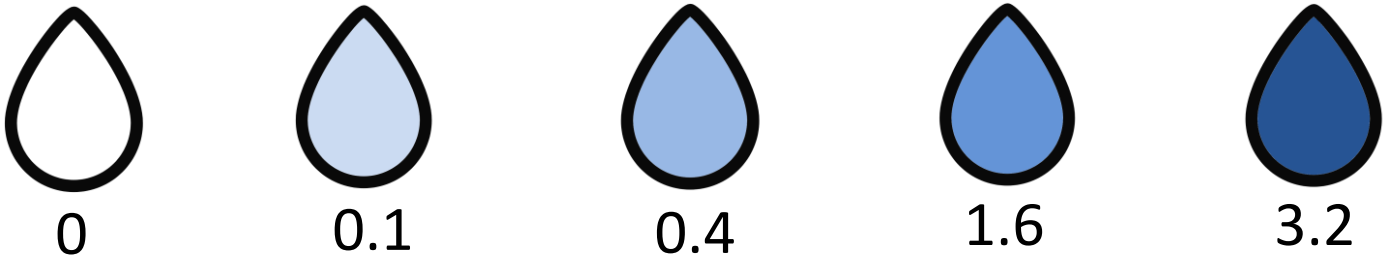
Decreased weight per litter and reduced weight change per litter

Body weight (F2)

Summarized from Luebker et al., 2005b

Key findings

mg/kg-d PFOS



Body weight (F0)

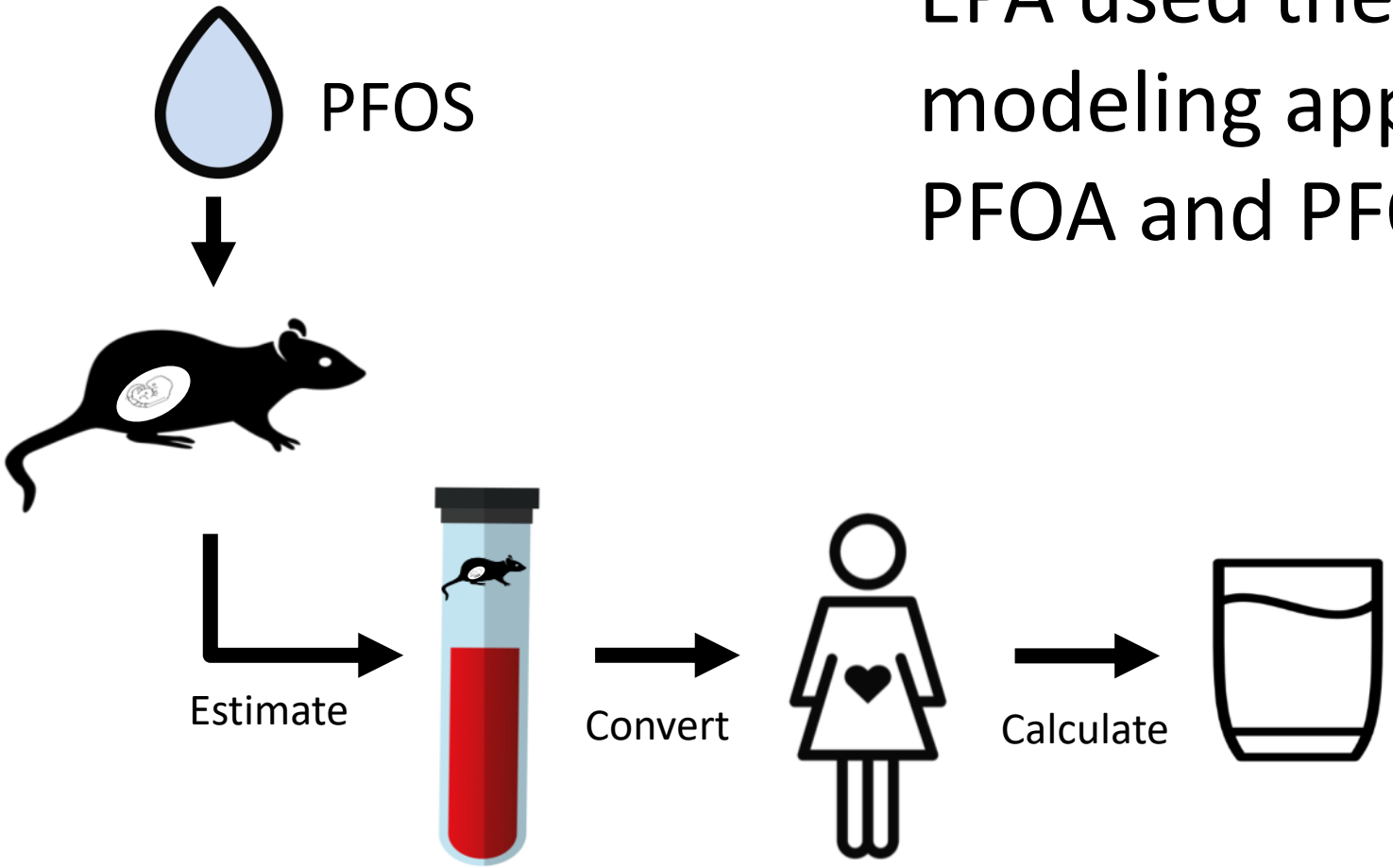
Survival (F1)

Body weight (F1)

Body weight (F2)

Summarized from Luebker et al., 2005b

EPA used the same modeling approach for PFOA and PFOS.



We have learned more PFOS since 2016.

PFOS can cross the placenta during pregnancy.

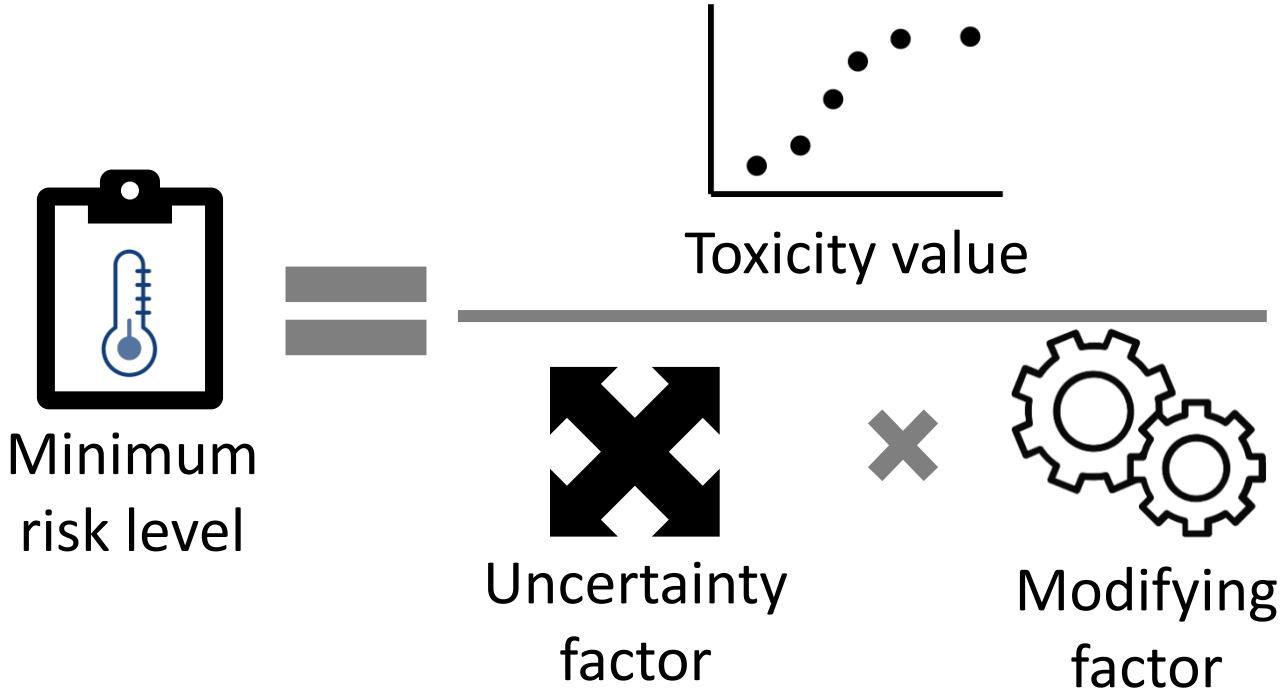
PFOS can pass through breastmilk.

PFOS may increase the risk for asthma, food allergies, and certain infectious diseases.

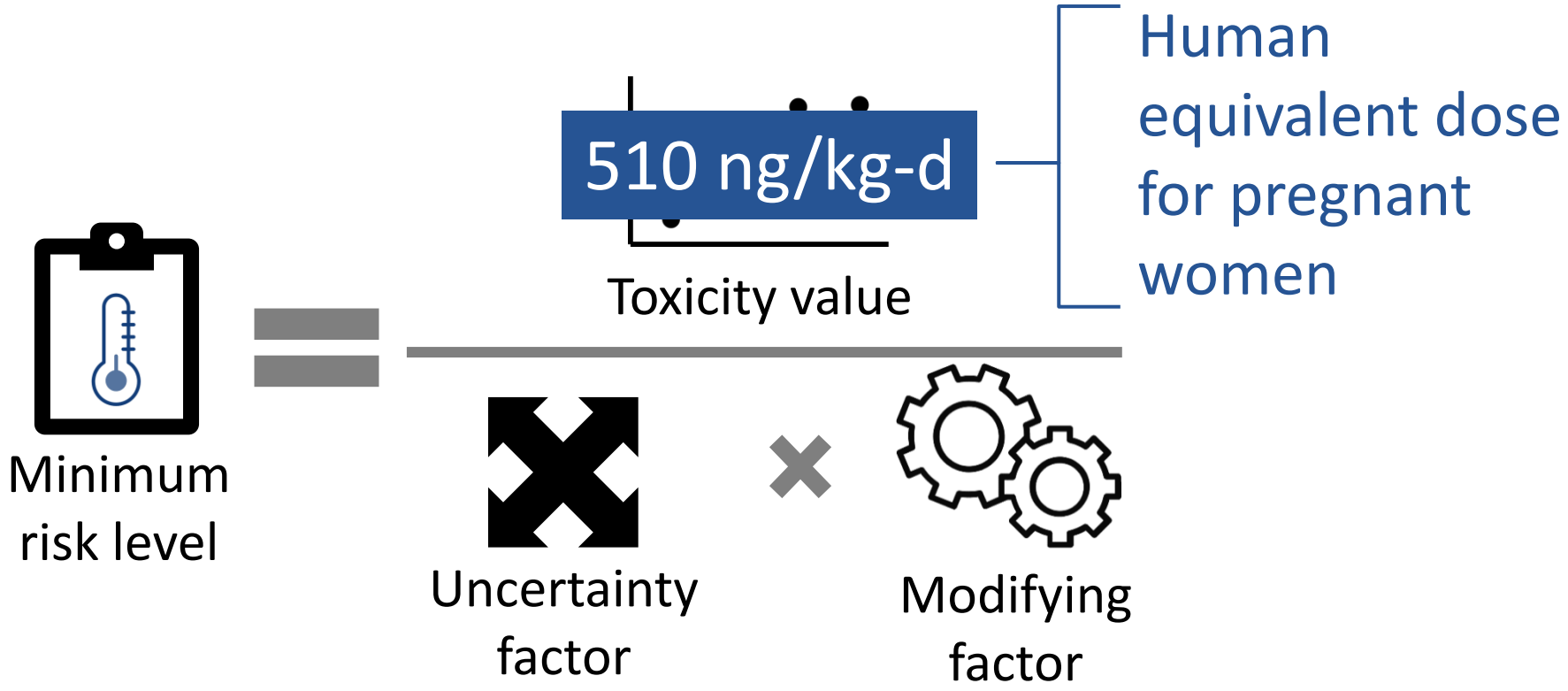
In 2018, ATSDR proposed a minimum risk level of 2 ng/kg-d for PFOS.

ATSDR = Agency for Toxic Substances and Disease Registry

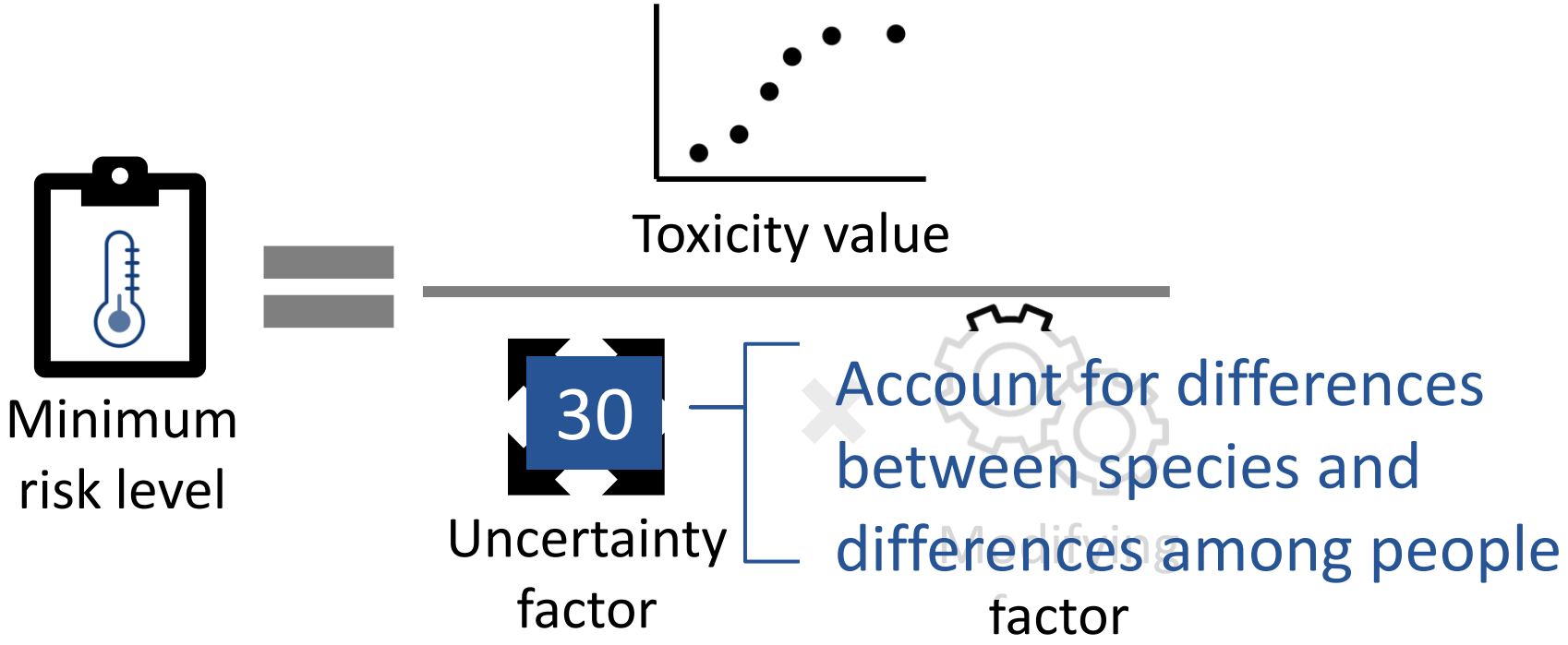
ATSDR's calculation for PFOS:



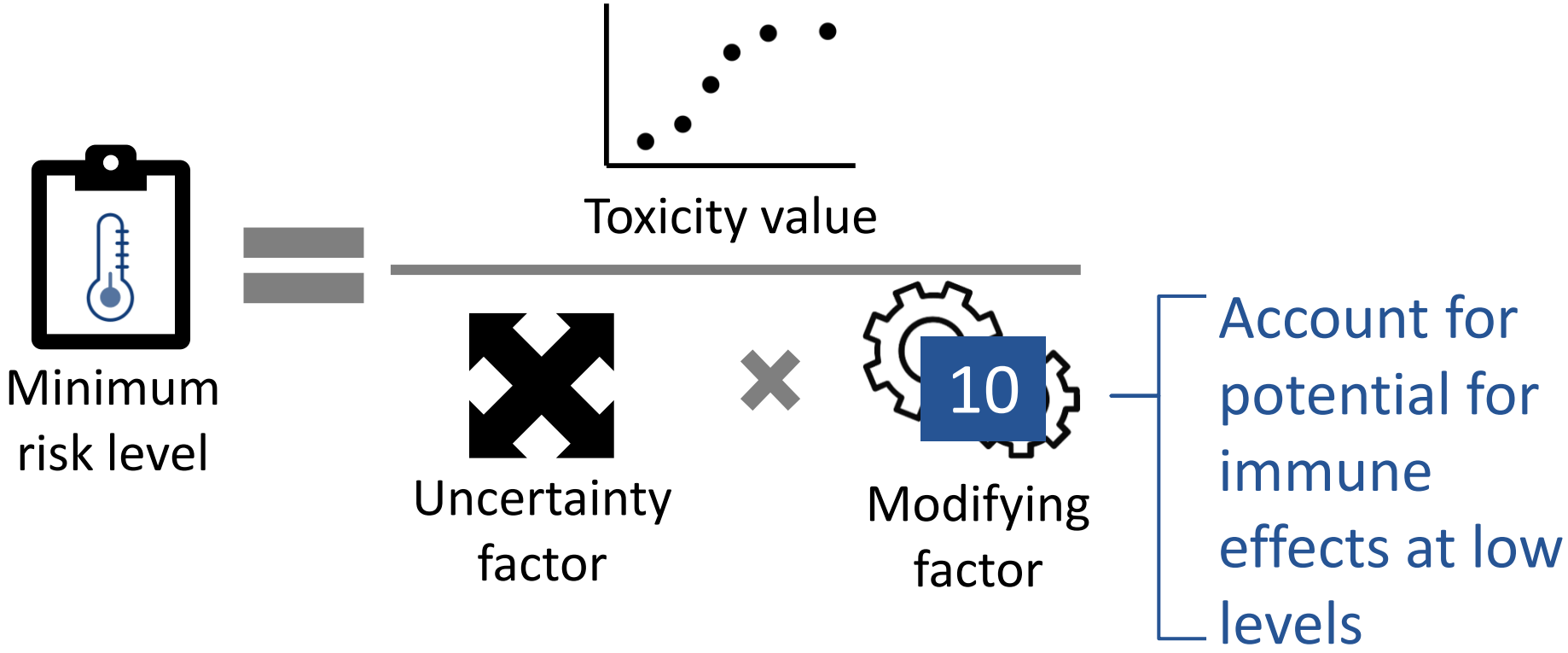
ATSDR's calculation for PFOS:



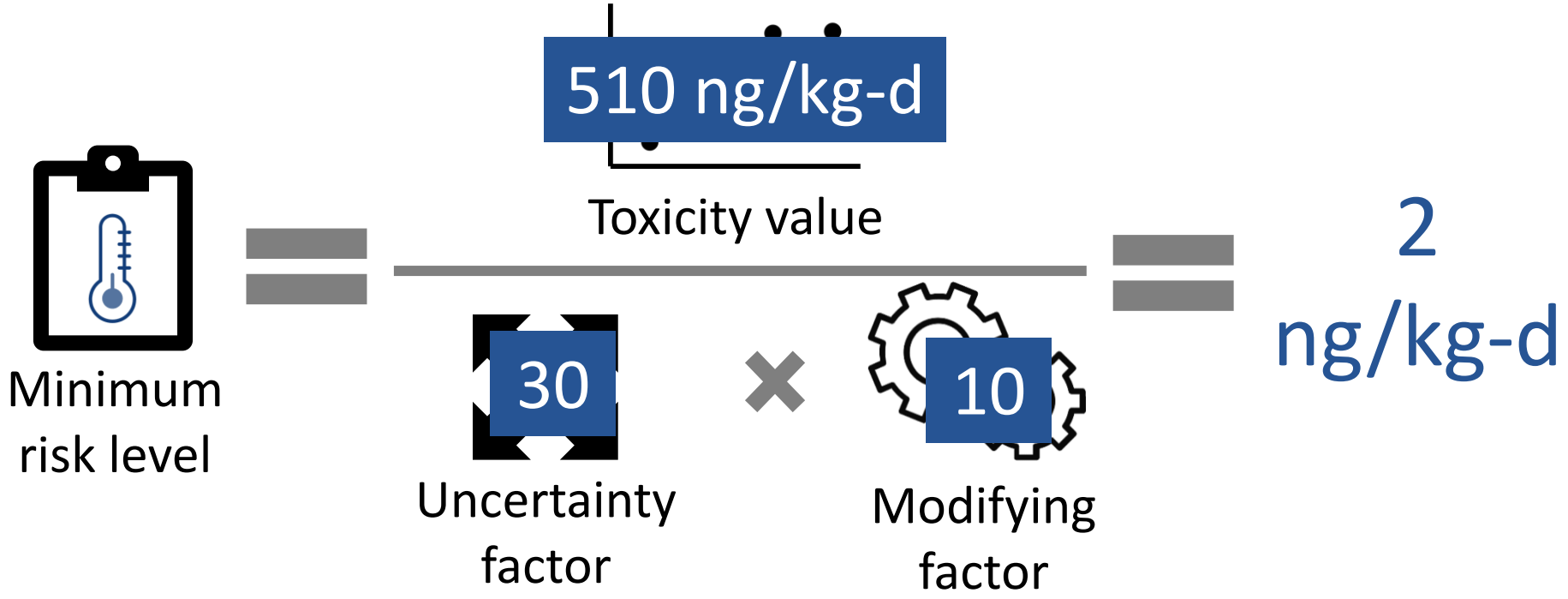
ATSDR's calculation for PFOS:



ATSDR's calculation for PFOS:

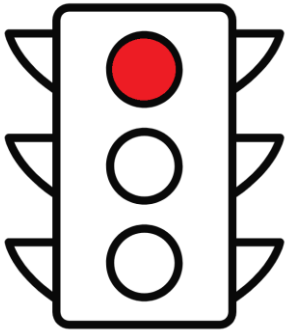


ATSDR's calculation for PFOS:



DHS recommends using ATSDR's minimum risk level for PFOS.

This approach protects from potential immune effects and infant exposure.

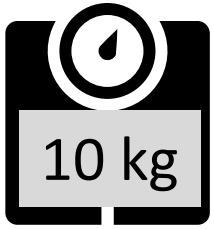


Enforcement Standard

=

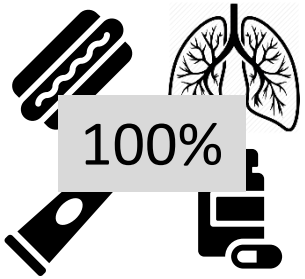
Acceptable daily intake

×

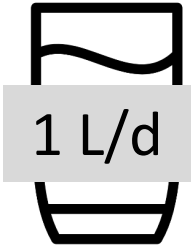


Body weight

×



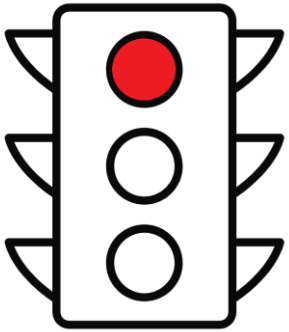
Relative source contribution



Water consumption

Specified in Statute

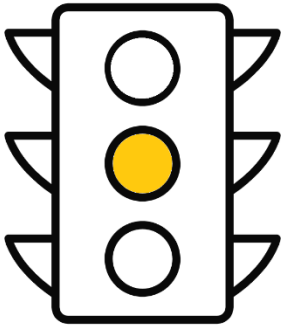
DHS' recommendation for PFOS



Enforcement Standard

= 20 ng/L

DHS' recommendation for PFOS



Preventive action limit

= 10%

PFOA has been shown to cause carcinogenic, teratogenic, or interactive effects

DHS recommends a combined enforcement standard of 20 ng/L for PFOA and PFOS.

Thanks!

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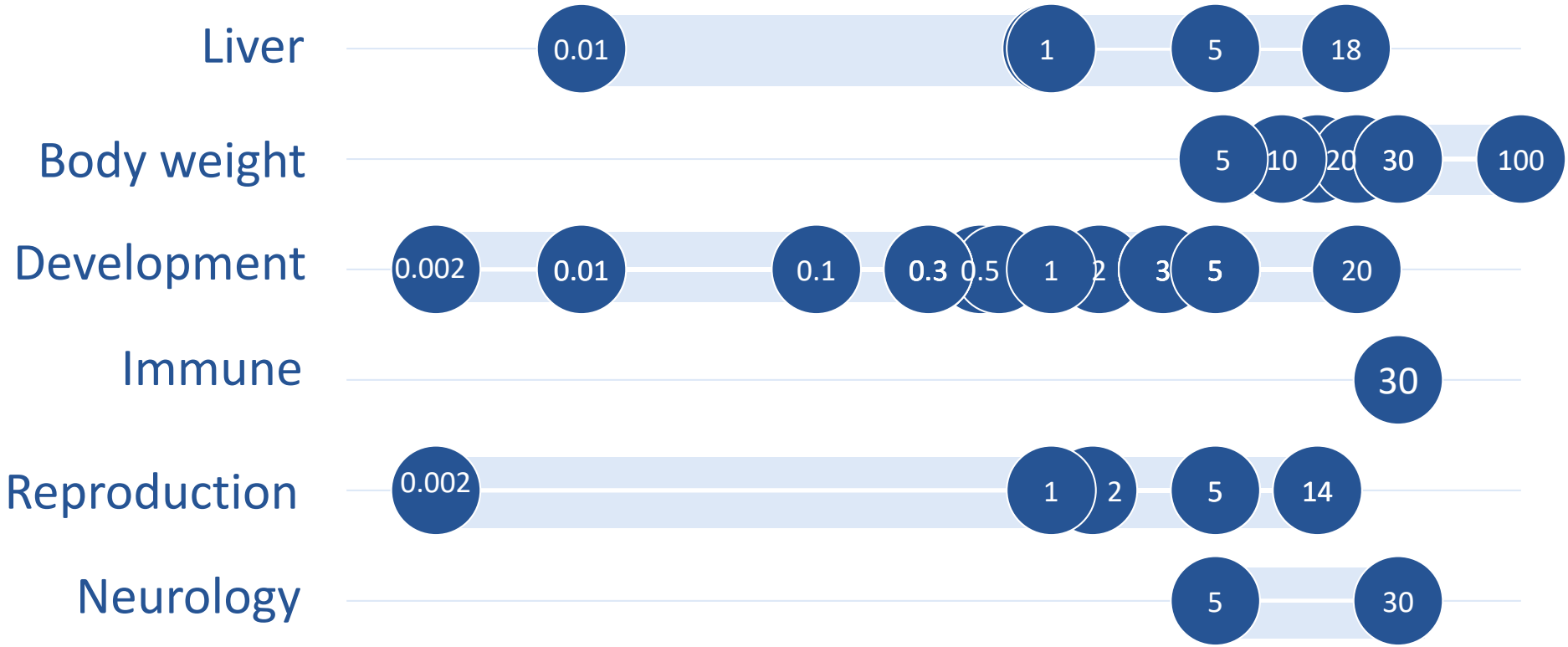
Additional information can be found on DHS' webpage: dhs.wisconsin.gov\water\gws.htm

The full scientific support document for all of the Cycle 10 compounds is available here: dhs.wisconsin.gov\publications\p02434v.pdf.

Additional information

LOAELs from non-acute studies



Data from Table 2-3 in ATSDR's Toxicological Profile for Perfluoroalkyls

Lau et al., 2006 results (part 1)

Effects observed in mothers		Dose (mg/kg-d) 1	3	5	10	20	40
Body weight	Reduced maternal weight gain					✓	✓
Reproduction	Increased percent of dams with full litter resorption			✓	✓	✓	✓
	Reduced number of live fetuses					✓	N/A
	Increased percent of prenatal loss					✓	N/A
	Increased time to parturition		✓		✓	✓	N/A

Lau et al., 2006 results (part 2)

Effects observed in offspring		Dose (mg/kg-d) 1	3	5	10	20
Survival	Reduced neonatal survival			✓	✓	✓
Body weight	Reduced fetal body weight					✓
Bone development	Decreased number of ossification sites in sternebrae, caudal vertebrae, metacarpals, metatarsals					✓
	Decreased number of ossification sites in forelimb proximal phalanges	✓	✓		✓	✓
	Decreased number of ossification sites in hindlimb proximal phalanges	✓			✓	✓
	Reduced percent ossification in calvaria	✓				✓
	Reduced percent ossification in supraoccipital				✓	✓
	Reduced percent ossification in unossified hybrid					✓
	Increased number of enlarged fontanel	✓	✓			✓

Summary of epidemiological studies located during the literature review for PFOS

Category	Examples	Number of Studies
Metabolic	Diabetes (type 1, 2, and gestational), glucose tolerance, insulin resistance, BMI, obesity/overweight, adiposity, cholesterol, triglycerides	41
Birth outcomes	Birth size (weight, length, etc), gestation age, small for gestational age, fetal growth, anogenital distance at birth	25
Neurological	Attention, impulse control, visual and spatial ability, cognitive development, executive function, autism spectrum disorder, intellectual disability	18
Reproductive	Endometriosis, preeclampsia, reproductive hormones, time to pregnancy, fertility, semen characteristics, pregnancy loss, menopause, puberty onset	13
Immune	Asthma, vaccine antibodies, allergic conditions, infectious disease incidence, atopic dermatitis	12
Thyroid	Thyroid hormones, thyroid function	10
Cardiovascular	heart attack, stroke, heart failure, arterial wall stiffness, coronary heart disease, blood pressure, hypertension	7
kidney	Chronic kidney disease, kidney function, glomerular filtration	7
Other	Vitamin D, bone density, lung function, dental carries, gut bacteria and metabolites, mortality,	6
DNA	Telomere length, DNA methylation	5
Liver	ALT (alanine aminotransferase), other liver function biomarkers	4
Cancer	Breast cancer	2

Lau et al., 2006 results (part 3)

Effects observed in offspring		Dose (mg/kg-d) 1	3	5	10	20
Birth defects	Increased percent of tail defects			✓	✓	✓
	Increased percent of limb defects			✓		✓
Heart	Increased percent of microcardia				✓	✓
Development	Delayed eye opening			✓	✓	✓
	Delayed vaginal opening		✓			✓
	Delayed first estrus			✓		✓
	Altered preputial separation	✓	✓	✓	✓	✓

Leubker et al., 2005 results (part 1)

Effects observed in F0 generation (males)		Dose (mg/kg-d) 0.1	0.4	1.6	3.2
Body weight	Reduced body weight			✓[a]	✓[b]
Food consumption	Reduced food consumption days 1-42			✓	✓
	Reduced food consumption days 56-63		✓	✓	✓

a. Days 56 through termination
b. Days 36 through termination

Leubker et al., 2005 results (part 2)

Effects observed in F0 generation (females)		Dose (mg/kg-d) 0.1	0.4	1.6	3.2
Body weight	Reduced body weight during precohabitation				✓c
	Reduced body weight during gestation			✓d	✓e
	Reduced body weight during lactation		✓f		✓g
Food consumption	Reduced food consumption during premating and gestation				✓
	Reduced food consumption during lactation			✓	N/A
Reproduction	Reduced gestation duration				✓
	Decreased implantation sites per delivered litter				✓
	Increased percent of animals with stillborn pups				✓
	Increased percent of animals with all pups dying (PND 1-4)				✓

c. Days 15-42
d. Gestation days 3-10
e. Gestation days 0-20Lactation day 7
f. Lactation day 1; no results for days 4-21

Leubker et al., 2005 results (part 3)

Effects observed in F1 generation		Dose (mg/kg-d) 0.1	0.4	1.6	3.2
Survival	Decreased liveborn				✓
	Increased stillborn per litter				✓
	Increased percent of pups found dead			✓[g]	✓[h]
	Reduced viability index			✓	✓
	Reduced lactation index			✓	N/A
Body weight	Decreased weight per litter			✓[i]	✓[j]
	Reduced weight change per litter			✓[k]	N/A

g. Postnatal days 2-4 and 5-7
h. Postnatal day 1 and 2-4; not results for days 5-21
i. Postnatal days 1-21
j. Postnatal day 1; no results for days 2-21
k. Postnatal days 1-4; 4-7; 7-14; 14-21

Leubker et al., 2005 results (part 3)

Effects observed in F2 generation		Dose (mg/kg-d) 0.1	0.4
Body weight	Reduced weight per litter		✓[l]
	Reduced weight change per litter		✓[m]

l. Postnatal days 7 and 14
m. Postnatal days 4-7 and 7-14