DNEL derivation and hazard summary

The derivation of DNELs is required for the chemical safety assessment (CSA) of substances manufactured/imported/used in quantities of 10 t/y and above.

The derivation of a DNEL for lifetime exposure from the minimum dataset required for the 10-100 t/y band, using default assessment factors in several extrapolation steps (including extrapolation for duration) involves considerable uncertainty. As further toxicological data are needed at each higher tonnage level, or become available in the scientific literature, more robust estimation of a DNEL becomes possible. DNELs should be reconsidered if further information becomes available.

Ammonium perrhenate 10-100 t/a

REACH tonnage-relevant data set:

Skin irritation/corrosion, *in vitro*:	non-irritant
Eye irritation, rabbit:	non-irritant
Acute oral LD_{50}, rats:	>2000 mg/kg bw
Acute inhalation LC_{50}	Not relevant route
Acute dermal LD_{50}, rats:	>2000 mg/kg bw [based on WoE]
Skin sensitisation, LLNA:	not a sensitiser
Ames test:	negative
In vitro micronucleus assay:	negative
In vitro mammalian cell gene mutation assay:	negative
Repeated dose toxicity	NOAEL = 110 mg/kg bw/day [OECD TG422]
Reproductive/Developmental toxicity	NOAEL = 110 mg/kg bw/day [OECD TG422*]

*OECD TG422 considered only a screening test for Reproductive/Developmental toxicity

DNELs - Workers

Acute toxicity – systemic effects

DNELs for acute toxicity should be derived if an acute toxicity hazard, leading to classification and labelling (i.e. under EU CLP or DSD regulations) has been identified and there is a potential for high peak exposures (this is only usually relevant for inhalation exposures). As no acute hazard has been identified, then a DNEL for acute toxicity is unnecessary. Long-term DNELs for systemic effects are expected to be sufficient to ensure that adverse effects do not occur. Consequently, no worker-DNEL for acute toxicity has been calculated.

Acute dermal – local effects:

Irritation/corrosion

In a reliable study, ammonium perrhenate gave no indication that it would be a significant skin irritant. No relevant data from acute and repeated dose toxicity studies are available. No worker-DNEL for skin irritation/corrosion has been calculated.

Sensitisation

In a reliable study, ammonium perrhenate gave no indication that it would be a significant skin sensitiser. No worker-DNEL for skin sensitisation has been calculated.

Acute inhalation – local effects:

Irritation/corrosion

There are no data in relation to respiratory tract irritation in humans or laboratory animals. However, the low skin and eye irritation potential of ammonium perrhenate suggests that this substance is unlikely to be a significant respiratory tract irritant. No relevant data from acute and repeated dose toxicity studies are available. No worker-DNEL for respiratory tract irritation/corrosion has been calculated.

Sensitisation

There are no data in relation to respiratory tract sensitisation in humans or laboratory animals. However, the lack of skin sensitisation potential of ammonium perrhenate suggests that this substance is unlikely to be a significant respiratory tract sensitiser. No worker-DNEL for respiratory tract sensitisation has been calculated.

Eyes – local effects

In reliable studies, ammonium perrhenate gave no indication that it would be a significant eye irritant. No relevant data from acute and repeated dose toxicity studies are available. [Generally there is no basis for quantitative assessment of eye irritation/corrosion and DNELs cannot be derived].

Long-term (repeated dose toxicity) – systemic effects

Oral

Not considered relevant for workers. No DNEL has been calculated.

Inhalation

Dose descriptor

There are no data available in humans or laboratory animals relating to repeated inhalation exposure to ammonium perrhenate. A reliable Repeated dose toxicity with

Reproductive/Developmental toxicity screening test (OECD TG422) by the oral route in rats is available and can be used in route-to-route extrapolation using appropriate modifications/assessment factors. In this study, a NOAEL for repeated dose toxicity of **110 mg/kg bw/day** was identified, with treatment at the next highest dose of 330 mg/kg bw/day associated with an increase in thyroid weight in both sexes, and a slight increased incidence of ploughing and excess salivation in males.

Mode-of-action

Available data indicate that ammonium perrhenate has only **threshold effects**. There is no evidence of genotoxicity. No data are available on carcinogenicity.

Modification of starting point

In the absence of any data to the contrary, the same bioavailability is assumed for humans and laboratory animals. As no data on effects of repeated inhalation exposure to ammonium perrhenate in humans or laboratory animals are available, route-to-route extrapolation to calculate a DNEL for such effects from the repeated dose oral toxicity study was considered a suitable alternative (no high first-pass metabolism has been reported or is expected).

In the absence of route-specific information on absorption for both the starting route (oral) and end route (inhalation), a default factor of 2 is recommended (which assumes 50% absorption for oral exposure, and 100% for inhalation). [110 mg/kg bw/day / 2 = **55 mg/kg bw/day**].

Workers are assumed to be exposed for 8 hours/day.

Converting oral data to a corresponding air concentration in the rat is required. The oral dose for the rat is converted to this corresponding air concentration using a standard breathing volume for the rat of 0.38 m^3/kg bw over 8 hours/day [exposure of workers]. Thus, 55 mg/kg bw/day / 0.38 m^3/kg bw/day = 145 mg/m^3 (8-hour exposure of workers). To account for the presumed light activity of workers, this value has been corrected for an increase in breathing volume, thus 145 mg/m^3 x (6.7 m^3 / 10 m^3) = **97.2 mg/m^3** (8-hour exposure of workers, light activity).

ECHA Assessment Factors (AF) for workers – inhalation DNEL (repeated dose toxicity, systemic effects)

Uncertainty	**AF**	**Justification for AF**
Interspecies differences	1	Default ECHA AF for rats for toxicokinetic differences in metabolic rate (allometric scaling); already considered in modification of starting point above
	2.5	Default ECHA AF for remaining toxicokinetic differences (not related to metabolic rate) and toxicodynamic differences

Uncertainty	AF	Justification for AF
Intraspecies differences	5	Default ECHA AF for (healthy) worker
Differences in duration of exposure	6	Default AF for subacute (28-day) to chronic extrapolation
Dose response and endpoint specific/severity issues	1	Default AF; human health relevant NOAEL from well-conducted 28-day dietary study. Effects at 330 mg/kg bw/day (increase in thyroid weight in both sexes, and a slight increased incidence of ploughing and excess salivation in males) were not considered severe
Quality of whole database	1	Default AF; the human health effects data are reliable and consistent, the available information meets the tonnage driven data requirements, and confidence in the database is high
Overall AF for worker	**75**	

- **Worker (light activity)-DNEL long-term for inhalation route-systemic** = 97.2 mg/m^3 / 75 = **1.3 mg/m^3**

Dermal

Dose descriptor

There are no data available in humans or laboratory animals relating to repeated dermal exposure to ammonium perrhenate. A reliable Repeated dose toxicity with Reproductive/Developmental toxicity screening test (OECD TG422) by the oral route in rats is available and can be used in route-to-route extrapolation using appropriate modifications/assessment factors. In this study, a NOAEL for repeated dose toxicity of **110 mg/kg bw/day** was identified, with treatment at the next highest dose of 330 mg/kg bw/day associated with an increase in thyroid weight in both sexes, and a slight increased incidence of ploughing and excess salivation in males.

Mode-of-action

Available data indicate that ammonium perrhenate has only **threshold effects**. There is no evidence of genotoxicity. No data are available on carcinogenicity.

Modification of starting point

In the absence of any data to the contrary, the same bioavailability is assumed for humans and laboratory animals. As no data on effects of repeated dermal exposure to ammonium perrhenate in

humans or laboratory animals are available, route-to-route extrapolation to calculate a DNEL for such effects from the repeated dose oral toxicity study was considered a suitable alternative (no high first-pass metabolism has been reported or is expected).

In the absence of route-specific information on absorption for both the starting route (oral) and end route (dermal), ECHA guidance on DNEL derivation (Characterisation of dose [concentration]-response for human health) indicates a default factor of 1, on the basis that, in general, dermal absorption will not be higher than oral absorption. [*REACH guidance for dermal absorption has default values of 10% and 100% for dermal absorption, although these are considered by HERAG not to be relevant for metals. HERAG guidance recommends values (reflective of full-shift exposure, i.e. 8-hours) for metal cations of 1% from exposure to liquid/wet media, and 0.1% from dry (dust) exposure. DNELs calculated on the basis of the ECHA default of 1 could be modified, as appropriate.*] [110 mg/kg bw/day / 1 = **110 mg/kg bw/day**].

Workers are assumed to be exposed for 8 hours/day.

ECHA Assessment Factors (AF) for workers – dermal DNEL (repeated dose toxicity, systemic effects)

Uncertainty	**AF**	**Justification for AF**
Interspecies differences	4	Default ECHA AF for rats for toxicokinetic differences in metabolic rate (allometric scaling)
	2.5	Default ECHA AF for remaining toxicokinetic differences (not related to metabolic rate) and toxicodynamic differences
Intraspecies differences	5	Default ECHA AF for (healthy) worker
Differences in duration of exposure	6	Default AF for subacute (28-day) to chronic extrapolation
Dose response and endpoint specific/severity issues	1	Default AF; human health relevant NOAEL from well-conducted 28-day dietary study. Effects at 330 mg/kg bw/day (increase in thyroid weight in both sexes, and a slight increased incidence of ploughing and excess salivation in males) were not considered severe
Quality of whole database	1	Default AF; the human health effects data are reliable and consistent, the available information meets the tonnage driven data requirements, and confidence in the database is high

Uncertainty	AF	Justification for AF
Overall AF for worker	**300**	

- **Worker-DNEL long-term for dermal route-systemic** = 110 mg/kg bw/day / 300 = **0.4 mg/kg bw/day**

This exposure is generally modelled as a dermal daily deposition in mg substance/cm^2 skin.

Long-term (repeated dose toxicity) – local effects

Dermal

There are no data to indicate that ammonium perrhenate is likely to cause significant local effects (e.g. irritation/corrosion and/or sensitisation) after repeated dermal exposure. No DNEL has been calculated.

Inhalation

There are no data to indicate that ammonium perrhenate is likely to cause significant local effects (e.g. irritation/corrosion and/or respiratory sensitisation) after repeated inhalation exposure. No DNEL has been calculated.

Reproductive toxicity (fertility impairment and developmental toxicity)

There was no indication from the Repeated dose toxicity with Reproductive/Developmental toxicity screening test (OECD TG422) of an adverse effect on fertility (at up to 1000 mg/kg bw/day), and therefore no fertility DNEL has been developed. A NOAEL of 110 mg/kg bw/day was identified for both maternal and potential developmental effects in rats given ammonium perrhenate by the oral route throughout mating, gestation and to day 4 of lactation. DNELs for developmental effects have been calculated.

Inhalation DNEL (development)

Dose descriptor

There are no data available in humans or laboratory animals relating to developmental effects following repeated inhalation exposure. The NOAEL of **110 mg/kg bw/day** derived from the screening assay (OECD TG422) by the oral route can be used in route-to-route extrapolation using appropriate modifications/assessment factors.

Mode-of-action

Available data indicate that ammonium perrhenate has only **threshold effects**. There is no evidence of genotoxicity. No data are available on carcinogenicity.

Modification of starting point

In the absence of any data to the contrary, the same bioavailability is assumed for humans and laboratory animals. As no data on developmental effects following repeated inhalation exposure to ammonium perrhenate in humans or laboratory animals are available, route-to-route extrapolation to calculate a DNEL for such effects from the OECD TG422 screening assay was considered a suitable alternative (no high first-pass metabolism has been reported or is expected).

In the absence of route-specific information on absorption for both the starting route (oral) and end route (inhalation), a default factor of 2 is recommended (which assumes 50% absorption for oral exposure, and 100% for inhalation). [110 mg/kg bw/day / 2 = **55 mg/kg bw/day**].

Workers are assumed to be exposed for 8 hours/day.

Converting oral data to a corresponding air concentration in the rat is required. The oral dose for the rat is converted to this corresponding air concentration using a standard breathing volume for the rat of 0.38 m^3/kg bw over 8 hours/day [exposure of workers]. Thus, 55 mg/kg bw/day / 0.38 m^3/kg bw/day = 145 mg/m^3 (8-hour exposure of workers). To account for the presumed light activity of workers, this value has been corrected for an increase in breathing volume, thus 145 mg/m^3 x (6.7 m^3 / 10 m^3) = **97.2 mg/m^3** (8-hour exposure of workers, light activity).

ECHA Assessment Factors (AF) for workers – inhalation DNEL (development)

Uncertainty	**AF**	**Justification for AF**
Interspecies differences	1	Default ECHA AF for rats for toxicokinetic differences in metabolic rate (allometric scaling); already considered in modification of starting point above
	2.5	Default ECHA AF for remaining toxicokinetic differences (not related to metabolic rate) and toxicodynamic differences
Intraspecies differences	5	Default ECHA AF for (healthy) worker
Differences in duration of exposure	1	No AF necessary as screening study covers critical period of organogenesis and to day 4 of lactation.
Dose response and endpoint specific/severity issues	1	Default AF; human health relevant NOAEL from well-conducted study. Effects at 330 mg/kg bw/day (decrease in pup viability over Days 1-4 of lactation) not considered severe and likely

Uncertainty	AF	Justification for AF
		associated with maternal toxicity.
Quality of whole database	2*	Additional AF to take account of the lower sensitivity of the screening study for reproductive/developmental effects
Overall AF for worker	**25**	

*Even were the maximum recommended additional AF of 5 used, the overall AF would be 62.5 (i.e. less than that for the Worker (light activity)-DNEL long-term for inhalation route-systemic).

- **Worker (light activity)-DNEL (development) long-term for inhalation route-systemic** = 97.2 mg/m^3 / 25 = **3.9 mg/m^3**

This inhalation DNEL (development) is higher than the inhalation DNEL for repeated dose effects (1.3 mg/m^3) and thus the long-term inhalation worker-DNEL for systemic effects is considered protective against developmental effects in pregnant workers.

Dermal DNEL (development)

Dose descriptor

There are no data available in humans or laboratory animals relating to developmental effects following repeated dermal exposure. The NOAEL of **110 mg/kg bw/day** derived from the screening assay (OECD TG422) by the oral route can be used in route-to-route extrapolation using appropriate modifications/assessment factors.

Mode-of-action

Available data indicate that ammonium perrhenate has only **threshold effects**. There is no evidence of genotoxicity. No data are available on carcinogenicity.

Modification of starting point

In the absence of any data to the contrary, the same bioavailability is assumed for humans and laboratory animals. As no data on developmental effects following repeated dermal exposure to ammonium perrhenate in humans or laboratory animals are available, route-to-route extrapolation to calculate a DNEL for such effects from the OECD TG422 screening assay was considered a suitable alternative (no high first-pass metabolism has been reported or is expected).

In the absence of route-specific information on absorption for both the starting route (oral) and end route (dermal), ECHA guidance on DNEL derivation (Characterisation of dose [concentration]-response for human health) indicates a default factor of 1, on the basis that, in general, dermal absorption will not be higher than oral absorption. [*REACH guidance for dermal absorption has default values of 10% and 100% for dermal absorption, although these are considered by HERAG not*

to be relevant for metals. HERAG guidance recommends values (reflective of full-shift exposure, i.e. 8-hours) for metal cations of 1% from exposure to liquid/wet media, and 0.1% from dry (dust) exposure. DNELs calculated on the basis of the ECHA default of 1 could be modified, as appropriate.] [110 mg/kg bw/day / 1 = **110 mg/kg bw/day**].

Workers are assumed to be exposed for 8 hours/day.

ECHA Assessment Factors (AF) for workers – dermal DNEL (development)

Uncertainty	**AF**	**Justification for AF**
Interspecies differences	4	Default ECHA AF for rats for toxicokinetic differences in metabolic rate (allometric scaling)
	2.5	Default ECHA AF for remaining toxicokinetic differences (not related to metabolic rate) and toxicodynamic differences
Intraspecies differences	5	Default ECHA AF for (healthy) worker
Differences in duration of exposure	1	No AF necessary as screening study covers critical period of organogenesis
Dose response and endpoint specific/severity issues	1	Default AF; human health relevant NOAEL from well-conducted study. Effects at 330 mg/kg bw/day (decrease in pup viability over Days 1-4 of lactation) not considered severe
Quality of whole database	2	Additional AF to take account of the lower sensitivity of the screening study for reproductive/developmental effects
Overall AF for worker	**100**	

- **Worker-DNEL (development) long-term for dermal route-systemic** = 110 mg/kg bw/day / 100 = **1.1 mg/kg bw/day**

This dermal DNEL (development) is higher than the dermal DNEL for repeated dose effects (0.4 mg/kg bw/day) and thus the long-term dermal worker-DNEL for systemic effects is considered protective against developmental effects in pregnant workers.

DNELs – General population exposed via the environment

Inhalation DNEL (repeated dose toxicity) – systemic effects

Dose descriptor

There are no data available in humans or laboratory animals relating to repeated inhalation exposure to ammonium perrhenate. A reliable Repeated dose toxicity with Reproductive/Developmental toxicity screening test (OECD TG422) by the oral route in rats is available and can be used in route-to-route extrapolation using appropriate modifications/assessment factors. In this study, a NOAEL for repeated dose toxicity of **110 mg/kg bw/day** was identified, with treatment at the next highest dose of 330 mg/kg bw/day associated with an increase in thyroid weight in both sexes, and a slight increased incidence of ploughing and excess salivation in males.

Mode-of-action

Available data indicate that ammonium perrhenate has only **threshold effects**. There is no evidence of genotoxicity. No data are available on carcinogenicity.

Modification of starting point

In the absence of any data to the contrary, the same bioavailability is assumed for humans and laboratory animals. As no data on effects of repeated inhalation exposure to ammonium perrhenate in humans or laboratory animals are available, route-to-route extrapolation to calculate a DNEL for such effects from the repeated dose oral toxicity study was considered a suitable alternative (no high first-pass metabolism has been reported or is expected).

In the absence of route-specific information on absorption for both the starting route (oral) and end route (inhalation), a default factor of 2 is recommended (which assumes 50% absorption for oral exposure, and 100% for inhalation). [110 mg/kg bw/day / 2 = **55 mg/kg bw/day**].

General population exposure via the environment is assumed to be continuous (24 hours/day, 7 days/week).

Converting oral data to a corresponding air concentration in the rat is required. The oral dose for the rat is converted to this corresponding air concentration using a standard breathing volume for the rat of 1.15 m^3/kg bw over 24 hours/day. Thus, 55 mg/kg bw/day / 1.15 m^3/kg bw/day = **47.8 mg/m^3** (24-hour exposure of the general population).

ECHA Assessment Factors (AF) for general population – inhalation DNEL (repeated dose toxicity, systemic effects)

Uncertainty	**AF**	**Justification for AF**
Interspecies differences	1	Default ECHA AF for rats for toxicokinetic differences in metabolic rate (allometric scaling);

Uncertainty	AF	Justification for AF
		already considered in modification of starting point above
	2.5	Default ECHA AF for remaining toxicokinetic differences (not related to metabolic rate) and toxicodynamic differences
Intraspecies differences	10	Default ECHA AF for general population (including children and the elderly)
Differences in duration of exposure	6	Default AF for subacute (28-day) to chronic extrapolation
Dose response and endpoint specific/severity issues	1	Default AF; human health relevant NOAEL from well-conducted 28-day dietary study. Effects at 330 mg/kg bw/day (increase in thyroid weight in both sexes, and a slight increased incidence of ploughing and excess salivation in males) were not considered severe
Quality of whole database	1	Default AF; the human health effects data are reliable and consistent, the available information meets the tonnage driven data requirements, and confidence in the database is high
Overall AF for general population	**150**	

- **General population-DNEL long-term for inhalation route-systemic** = 47.8 mg/m^3 / 150 = **0.3 mg/m^3**