# Derived No Effect Levels (DNELs) of N-Vinyl Caprolactam (NVC) (CAS# 2235-00-9)

# For Toxicological Risk Assessments by the EuPIA Member Companies

***Derived No Effect Levels (DNELs) of NVC***

| **Occupational Exposure (Workers)** | **DNEL Values** |
|---|---|
| Local effects - Inhalation | 0.10 mg/m$^3$ |
| Long term exposure - Inhalation | 1.16 mg/m$^3$ |
| Long term exposure - Dermal | 0.42 mg/kg bw/day |
| Long term exposure - Oral | Not applicable |
| **General Population** | |
| Local effects - Inhalation | 0.018 mg/m$^3$ |
| Long term exposure - Inhalation | 0.21 mg/m$^3$ |
| Long term exposure - Dermal | 0.15 mg/kg bw/day |
| Long term exposure - Oral | 0.17 mg/kg bw/day |

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## 1. Summary

N-Vinylcaprolactam (NVC) (CAS# 2235-00-9, EC# 218-787-6), aka 1-vinylhexahydro-2H-azepin-2-one is used as a binder in the EuPIA member companies manufactured printing inks for non-food and pharmaceutical packaging applications.

Due to new toxicological data generated for the registration according to REACH (Regulation (EC) 1907/2006) downstream users were advised in 2014 to change the classification and labelling of NVC. The new hazard classification of NVC for according to the Classification, Labelling and Packaging (CLP) Regulation (EC) 1272/2008 is "H372: STOT RE, Category 1 (Causes damage to liver, respiratory tract through prolonged or repeated exposure); H302: Acute Toxicity, Category 4 (Oral) (Harmful if swallowed); H312: Acute Toxicity, Category 4 (Dermal) (Harmful in contact with skin); H317: Skin Sensitizer, Category 1B (May cause an allergic skin reaction) and H319: Eye Irritation, Category 2 (Causes serious eye irritation)".

STOT RE, Category 1 (H372) hazard is listed as "Group B" category of the existing EuPIA Exclusion Policy and by default EuPIA members are expected to substitute respective hazard classified substances or mixtures as soon as practicable (EuPIA, 2025). However, a recent proposal of considering a risk-based over hazard-based approach will enable the printing ink manufacturers to perform comprehensive risk assessments for those substances or mixtures classified with the CLP hazard classes/categories listed in Group A and Group B of EuPIA exclusion policy and having a threshold based (non-linear) dose response. NVC was selected for the proof of concept to assess the feasibility of the risk-based approach, and accordingly its Derived No-Effect Level (DNEL) values are derived by this EuPIA member company. Different DNELs were derived for NVC reflecting the likely routes of exposure while using this substance in the printing inks, i.e., manufacturing of inks, printshops and consumers. These DNEL values of NVC will be considered for the risk assessments to be performed for the by the EuPIA member companies to demonstrate the safe use of this substance in the printing inks.

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### 1.1. N-Vinylcaprolactam (NVC) Toxicology Profile

NVC is a light yellow crystalline liquid with a melting point of 30 °C, boiling point of 250.4 °C at 1013.25 Pa, and relative density of 1.02184 g/cm$^3$ at 20 °C. The saturated vapour pressure of 2-NVC at a temperature of 20 °C is equal to 0.03 hPa. It has a flash point of 114 °C at 1013.25 hPa and non-flammable (ECHA CHEM Dossier).

NVC is expected to absorb by the oral, dermal and inhalation routes with likely distribution through extracellular body fluids. The formation of reactive metabolites is unlikely. Excretion will most likely occur via the urine and no bioaccumulation in the body is expected.

The acute oral and dermal $LD_{50}$ of NVC was found to be 1114 mg/kg bw in rats and 1700 mg/kg bw in rabbits, respectively. The acute inhalation $LC_{50}$ was determined to be >1.6 mg/L in rats. Based on a number of reliable skin and eye irritation studies in rabbits, NVC was found to be non-irritating to skin but irritating to eyes. It is found to be a moderate skin sensitizer in the mice Local Lymph Node Assay (LLNA) with an EC3 value of 9.0% (w/w). No data on respiratory sensitization was found for NVC, but there are no structural alerts for such properties (ECHA CHEM Dossier).

Number of reliable repeated dose oral toxicity studies are available for NVC. In a repeated dose 28-day oral toxicity study in Sprague Dawley rats conducted as per OECD 407 guideline, 50, 250, and 500 mg/kg bw/day of NVC was administered orally for 28 days followed by a 14 days recovery period. No mortality was observed, however, rats treated with 250 and 500 mg/kg bw/day showed signs of increased salivation, decrease in body weights, increase in clotting time, creatinine and urea, reduction in kidney weight and increase in liver weights. A NOAEL of 50 mg/kg bw/day was derived from this study. In a sub-chronic oral toxicity in rats conducted as per OECD 408 guideline, NOAEL of 130 mg/kg bw/day was derived for male rats from a 90-day oral (gavage) administration. The lowest observed adverse effect level (LOAEL) for systemic toxicity derived from this study was 260 mg/kg bw/day for male rats and 130 mg/kg bw/day for female rats (ECHA CHEM Dossier).

In a sub-acute inhalation toxicity study conducted as per OECD 412 guideline, 1, 6, 58 or 173 mg/m$^3$ of NVC vapors was subjected for whole body exposure to wistar rats for 28 days, 6 hours/day and 5 days/week. Treatment-related findings were observed in the nasal cavity in all levels and in the liver of males and females. Minimal hypertrophy of centrilobular cells and degeneration/regeneration of the olfactory epithelium in the nasal cavity was observed. A systemic NOAEC of 58 mg/m$^3$ and local NOAEC of 1 mg/m$^3$ was derived from this study.

In a sub-chronic inhalation toxicity study conducted as per OECD 413 guideline, 0.0059, 0.058, 0.181 mg/l (1, 10, 32 ppm) of NVC vapors was subjected for whole body exposure to wistar rats for 90 days, 5 hours/day and 5 days/week. Treatment-related findings were observed in the nasal and oral cavity and in slight systemic toxicity in the high dose group (32 ppm). The systemic effects were substantiated by clinical pathological findings of mild anemia, adaptive response of the liver and probably slight disturbance of renal tubular function. Nasal irritation and liver changes were found. No systemic toxicity was observed in rats exposed to 10 or 1 ppm, but nasal irritation was detectable by histopathology in a dose-dependent manner at both dose levels. NOAEC for systemic toxicity was found to be 58 mg/m$^3$ (0.058 mg/l; 10 ppm) for NVC under this experimental conditions (ECHA CHEM Dossier).

Based on these toxicity findings, in January 2014, REACH has advised downstream users to update the hazard classification of NVC as “H372: STOT RE, Category 1 (Causes damage to liver, respiratory tract through prolonged or repeated exposure)” along with “H302: Acute Toxicity, Category 4 (Oral) (Harmful if swallowed), H312: Acute Toxicity, Category 4 (Dermal) (Harmful in contact with skin), H317: Skin Sensitizer, Category 1B (May cause an allergic skin reaction) and H319: Eye Irritation, Category 2 (Causes serious eye irritation)”.

NVC was found to be non-mutagenic in a bacterial reverse mutation assay in Salmonella and E.coli (OECD 471, Ames) and in the HPRT assay (OECD 476, In vitro Mammalian Cell Gene Mutation Test). It was non-clastogenic in the Chromosome Aberration Test (OECD 473, In vitro Mammalian Chromosome Aberration Test). Based on these in vitro study results, NVC is not subject to mutagenic classification as per CLP Regulation (EC) No 1272/2008.

In a reproduction/developmental screening study conducted as per OECD 422 guideline, NVC was administered daily as an aqueous preparation to groups of 10 male and 10 female Wistar rats (F0 animals) by gavage at doses of 40, 120 and 400 mg/kg bw/day. The duration of treatment covered a 30 days in-life period in the males (including premating, mating [mating pairs were from the same test group] and post-mating period) and a 2-weeks premating and mating period, the entire gestation and approximately 3 weeks of lactation period in the females. Systemic toxicity, such as piloerection, reduced attention, semi-closed eyelids as well as reduction in food consumption, body weight loss and decrease in body weight gain, altered clinical pathology parameters and further histopathological findings down to the mid-dose level of 120 mg/kg bw/day were observed. NOAEL for general systemic toxicity was found to be 40 mg/kg bw/day. NOAEL for fertility and reproductive performance was set to 400 mg/kg bw/day (high-dose level) for male and female wistar rats. The NOAEL for developmental toxicity was the mid-dose level of 120 mg/kg bw/day based on the lower viability index and reduced pup growth at the highest dose level (400 mg/kg bw/day) (ECHA CHEM Dossier).

In a prenatal developmental toxicity study conducted as per OECD 414 guideline, NVC was administered as an aqueous preparation to groups of 25 time-mated female wistar rats by gavage at dose levels of 20, 80 and 240 mg/kg bw/day on gestation days (GD) 6 through 19. Evidence of distinct maternal toxicity, such as reduction in food consumption, body weight loss after initiation of treatment, decrease in (corrected) body weight gain as well as altered biochemical parameters down to the mid-dose level of 80 mg/kg bw/day were reported. NOAEL of 20 mg/kg bw/day was reported for maternal toxicity and 80 mg/kg bw/day for prenatal developmental toxicity (ECHA CHEM Dossier). Available repeated dose toxicity studies performed with N-Vinylcaprolactam revealed no effects on reproductive organs. Therefore, classification for reproductive toxicity is not warranted according to EU Directive 67/548 EEC and EU Classification, Labelling and Packaging of Substances and Mixtures (CLP) Regulation (EC) No 1272/2008.

NVC is not listed in the Swiss Ordinance of the FDHA on articles and materials (RS 817.023.21 (Swiss Ordinance, 2024).

### 1.2. Derivation of Derived No Effect Levels (DNELs)

For derivation of DNELs, all available hazard information of NVC was evaluated. Hyperplasia of the respiratory epithelium in the nasal cavity and hypertrophy of centrilobular liver cells are the main effects which were observed in the repeated dose inhalation toxicity studies in rats for NVC. Increased salivation, decrease in body weights, increase in clotting time, creatinine and urea, reduction in kidney weight and increase in liver weights are the critical effects which were observed in the repeated dose oral toxicity studies in rats for NVC.

NOAEC of 58 mg/m³ derived form a 90-day repeated dose inhalation toxicity study in wistar rats

and general systemic toxicity NOAEL of 40 mg/kg bw/day derived from reproduction/developmental screening study in wistar rats were considered as the most sensitive dose descriptors to establish the DNEL values for inhalation, dermal and oral routes of exposure for NVC. Further, local NOAEC of 1 mg/m³ derived from a 28-day repeated dose inhalation toxicity study in wistar rats due to the hyperplasia of the respiratory epithelium was considered for the derivation of DNEL for local effects due to long term exposure.

The following DNEL values were established for NVC for workers and general population covering inhalation, dermal and oral routes as per "ECHA guidance on information requirements and chemical safety assessment, Chapter R.8: Characterisation of dose [concentration]-response for human health " on Characterisation of dose [concentration]-response for human health" (ECHA, 2012) and "ECTOC. Guidance on Assessment Factors to Derive a DNEL (ECTOC 2014).

## Workers:

**DNEL long-term for inhalation route-systemic:**

DNEL (mg/m$^3$)= Corrected NOAEC / Assessment Factors (AF)

NOAEC = 58 mg/m³ (90-day inhalation toxicity study (OECD 413)) (ECHA CHEM)

Corrected NOAEC = NOAEC x (Exposure duration of the study (h)/ Exposure duration of workers (h)) x ($sRV_{human}$/wRV)

Corrected NOAEC = 58 mg/m³ x ((6h/d)/(8h/d)) x (6.7 m³ (8h)/10 m³ (8h)) = 29.1 mg/m3

Overall Assessment Factors (AF) = 2.5 x 5 x 2 x 1 x 1 = 25

Interspecies differences =2.5*

Intraspecies differences = 5

Exposure duration = 2 (sub-chronic to chronic)

Dose-response = 1

Quality of database = 1

- Allometric scaling factor of 4 is not applied, because the ventilation rate directly depends on the basal metabolic rate.

**Worker DNEL long-term for inhalation route-systemic = Corrected NOAEC / Overall Assessment Factors (AF) = 29.1 / 25 = 1.16 mg/m³.**

**DNEL long-term for inhalation route-local effects:**

DNEL (mg/m$^3$)= Corrected NOAEC / Assessment Factors (AF)

NOAEC = 1.0 mg/m³ (28-day inhalation toxicity study (OECD 412)) (ECHA CHEM)

Corrected NOAEC = NOAEC x (Exposure duration of the study (h)/ Exposure duration of workers (h)) x ($sRV_{human}$/wRV)

Corrected NOAEC = 1.0 mg/m³ x ((6h/d)/(8h/d)) x (6.7 m³ (8h)/10 m³ (8h)) = 0.50 mg/m$^3$

Overall Assessment Factors (AF) = 1 x 5 x 1 x 1 x 1 = 5

Interspecies differences = 1*
Intraspecies differences = 5
Exposure duration = 1$^{\#}$

Dose-response = 1

Quality of database = 1

- Allometric scaling factor of 4 is not applied, because the ventilation rate directly depends on the basal metabolic rate. Additional factor of 2.5 was not applied as there is no additional evidence for species differences including toxicodynamics.

# Irritation responses are considered to be mostly concentration dependent and no duration-based difference between sub-acute and chronic exposure is assumed.

**Worker DNEL long-term for inhalation route-local = Corrected NOAEC / Overall Assessment Factors (AF)= 0.50 / 5 = 0.10 mg/m$^3$.**

**DNEL long-term for dermal route-systemic:**

There is no toxicity data on repeated exposure by the dermal route. Hence the worker DNEL long-term for dermal route - systemic is derived from the NOAEC of 58 mg/m³ obtained in the sub-chronic inhalation repeated dose toxicity study in wistar rats.

NOAEC = 58 mg/m³ (90-day inhalation toxicity study (OECD 413) (ECHA CHEM)

$NOAEL_{dermal}$ = $NOAEC_{inhalation}$ x sRVRat x $ABS_{inhalation\text{-}rat}/ABS_{dermal\text{-}human}$ = 58 mg/m3 x 0.29 m3/kg bw x 1 = 16.8 mg/kg bw/day.

Overall Assessment Factors (AF) = 4 x 5 x 2 x 1 x 1 = 40

Interspecies differences = 4*

Intraspecies differences = 5

Exposure duration = 2 (sub-chronic to chronic)

Dose-response = 1

Quality of database = 1

Worker DNEL long-term for dermal route-systemic = $NOAEL_{dermal}$ / Overall Assessment Factors (AF) =16/ 40 = 0.42 mg/kg bw/day

- Interspecies differences are fully covered by the allometric scaling. The DNEL is derived from the most sensitive endpoint with the lowest NOAEC observed in a mechanistic study. There is no additional evidence for species differences including toxicodynamics, hence no additional factor is used.

**DNEL long-term for oral route-systemic: Not applicable for workers**

**Acute/short term exposure: No hazard identified for NVC**

## General Population:

**DNEL long-term for inhalation route-systemic:**

DNEL (mg/m$^3$)= Modified NOAEC / Assessment Factors

NOAEC = 58 mg/m³ (90-day inhalation toxicity study (OECD 413)) (ECHA CHEM)

Corrected NOAEC = NOAEC x (Exposure duration of the study/day (h)/ Exposure duration of general population/day (h) x (Exposure duration of the study/week (d)/ Exposure duration of general population/week (d))

Corrected NOAEC = 58 mg/m³ x (6h/d)/(24h/d) x (5d/7d) = 10.4 mg/m³

Overall Assessment Factors (AF) = 2.5 x 10 x 2 x 1 x 1 = 50

Interspecies differences = 2.5* Intraspecies differences = 10

Exposure duration = 2 (sub-chronic to chronic) Dose-response = 1

Quality of database = 1

- Allometric scaling factor of 4 is not applied, because the ventilation rate directly depends on the basal metabolic rate.

**General Population DNEL long-term for inhalation route-systemic = Corrected NOAEC / Overall Assessment Factors (AF) = 10.4 / 50 = 0.21 mg/m³**

**DNEL long-term for inhalation route-local effects:**

DNEL (mg/m³)= Modified NOAEC / Assessment Factors

NOAEC = 1.0 mg/m³ (28-day inhalation toxicity study (OECD 412)) (ECHA CHEM)

Corrected NOAEC = NOAEC x (Exposure duration of the study/day (h)/ Exposure duration of general population/day (h) x (Exposure duration of the study/week (d)/ Exposure duration of general population/week (d))

Corrected NOAEC = 1.0 mg/m³ x (6h/d)/(24h/d) x (5d/7d) = 0.18 mg/m3

Overall Assessment Factors (AF) = 1 x 10 x 1 x 1 x 1 = 10

Intraspecies differences = 10*

Exposure duration = 1#

Dose-response = 1

Quality of database = 1

- Allometric scaling factor of 4 is not applied, because the ventilation rate directly depends on the basal metabolic rate. Additional factor of 2.5 was not applied as there is no additional evidence for species differences including toxicodynamics.

# Irritation responses are considered to be mostly concentration dependent and no duration-based difference between sub-acute and chronic exposure is assumed.

**General Population DNEL long-term for inhalation route-local = Corrected NOAEC / Overall Assessment Factors (AF) = 0.18 / 10 = 0.018 mg/m³**

**DNEL long-term for dermal route-systemic:**

There is no toxicity data on repeated exposure by the dermal route. Hence the worker DNEL long-term for dermal route - systemic is derived from the NOAEC of 58 mg/m³ obtained in the sub-chronic inhalation repeated dose toxicity study in wistar rats.

NOAEC = 58 mg/m³ (90-day inhalation toxicity study (OECD 413)) (ECHA CHEM)

$NOAEL_{dermal}$ = $NOAEC_{inhalation}$ x $sRV_{Rat}$ x ($ABS_{inhalation\text{-}rat}/ABS_{dermal\text{-}human}$) x (Exposure duration of the study/week (d)/ Exposure duration of general population/week (d)) = 58 mg/m³ x 0.29 m³/kg bw x 1 x (5d/7d) = 12.0 mg/kg bw/day.

Overall Assessment Factors (AF) = 4 x 10 x 2 x 1 x 1 = 80 Interspecies differences = 4*

Intraspecies differences = 10

Exposure duration = 2 (sub-chronic to chronic) Dose-response = 1

Quality of database = 1

General Population DNEL long-term for dermal route-systemic = $NOAEL_{dermal}$ / Overall Assessment Factors (AF) = 12.0 / 80 = 0.15 mg/kg bw/day

- Interspecies differences are fully covered by the allometric scaling. The DNEL is derived from the most sensitive endpoint with the lowest NOAEC observed in a mechanistic study. There is no additional evidence for species differences including toxicodynamics, hence no additional factor is used.

**DNEL long-term for oral route-systemic:**

NOAEL = 40 mg/kg bw/day (Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test (OECD 422)) (ECHA CHEM)

Overall Assessment Factors (AF) = 4 x 10 x 6 x 1 x 1 = 240

Intraspecies differences = 10

Exposure duration = 6 (sub-acute to chronic)

Dose-response = 1

Quality of database = 1

General Population DNEL long-term for oral route-systemic = NOAELoral / Overall Assessment Factors (AF) = 40 / 240 = 0.17 mg/kg bw/day

- Interspecies differences are fully covered by the allometric scaling. There is no additional evidence for species differences including toxicodynamics. Therefore, no additional factor is used.

**Acute/short term exposure: No hazard identified**

## 2. Conclusion

The following is the summary of the DNEL values of NVC established for workers and general population covering inhalation, dermal and oral routes:

***Summary of Derived No Effect Levels (DNELs) of NVC***

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| Long term exposure - Oral | mg/kg bw/day |

## Appendices

### Appendix 1 - References

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