United States
Environmental Protection Agency

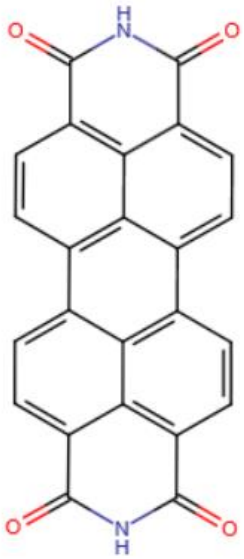
Office of Chemical Safety and
Pollution Prevention

# Final Risk Evaluation for C.I. Pigment Violet 29 (Anthra[2,1,9-def:6,5,10-d'e'f']diisoquinoline-1,3,8,10(2H,9H)-tetrone)

## Systematic Review Supplemental File:

## Data Quality Evaluation of Human Health Hazard Studies

## CASRN: 81-33-4




*January 2021*

This document is a compilation of tables for the data extraction and evaluation for C.I. Pigment Violet 29 (CASRN 81-33-4). Each table shows the data point or set or information element that was extracted and evaluated from a data source in accordance with Appendix D of the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018). If the source contains more than one data set or information element, the review provides an overall confidence score for each data set or information element that is found in the source. Therefore, it is possible that a source may have more than one overall quality/confidence score.

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**Table 1. Acute Oral Toxicity Study with Rats, (BASF, 1975b)**

| Study Reference: | **BASF. 1975. Acute oral toxicity with rats. BASF Report XXV/454. Product Safety Basel, BASF Schweiz AG, Switzerland.[as reported in Translated PV29 Tox Summaries, Product Safety Basel, BASF Schweiz AG, Switzerland, January 31, 2018]. HERO ID: 4731529.** | | | | | |
|---|---|---|---|---|---|---|
| **Note:** | Study guideline was not indicated in the study report | | | | | |
| **Domain** | **Metric** | **Qualitative Determination [*i.e.*, High, Medium, Low, Unacceptable, or Not rated]** | **Comments** | **Metric Score** | **Metric Weighting Factor** | **Weighted Score** |
| **Test Substance** | 1. Test substance identity | Medium | CASRN number was provided (81-33-4) but other expected details were not discussed in the study. For instance, the physical nature of the test substance was not described but it is inferred to be solid state based on the physical/chemical properties of PV29. | 2 | 2 | 4 |
| | 2. Test substance source | Low | No details were provided about the source and lot number of the test substance. | 3 | 1 | 3 |
| | 3.Test substance purity | Low | No details were provided about the test substance purity. | 3 | 1 | 3 |
| **Test setup** | 4. Negative controls | Low | A concurrent negative control group was not reported. It is inferred that the laboratory did not include the negative control because water (vehicle) would not be triggering a response. | 3 | 2 | 6 |
| | 5. Positive controls | Not rated | Not rated/applicable - Positive controls are not necessary for this study type. | NR | NR | NR |
| | 6. Randomized allocation | Low | The study report did not state how animals were | 3 | 1 | 3 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | allocated to study groups. | | | |
| **Exposure characterization** | 7. Preparation and storage of test substance | Low | Test substance is likely poorly soluble in water based on the physicochemical properties of the CASRN. The study report states that the test substance was prepared as a 50% aqueous suspension in water; however, no details were provided on test substance preparation (*e.g.*, stirring, and whether homogenous when administered) and it is not evident that the aqueous suspension was homogenous when dosing was performed. | 3 | 1 | 3 |
| | 8. Consistency of Exposure administration | Low | Details of exposure administration were not fully addressed. The study report states that a single dose was administered via gavage to each animal; however, the dosing volume was not reported so it is not evident that exposure administration was the same for all animals. | 3 | 1 | 3 |
| | 9. Reporting of doses / concentrations | High[A] | | 1 | 2 | 2 |
| | 10. Exposure frequency and duration | High[A] | | 1 | 1 | 1 |
| | 11. Number of exposure groups and dose spacing | High[A] | | 1 | 1 | 1 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 12. Exposure route and method | High[A] | | 1 | 1 | 1 |
| **Test organisms** | 13. Test animal characteristics | Medium | Health status and age at initiation were not reported. | 2 | 2 | 4 |
| | 14. Adequacy and consistency of animal husbandry conditions | Low | Study provided minimal information on the adequacy of animal husbandry conditions. | 3 | 1 | 3 |
| | 15. Number per group | High[A] | | 1 | 1 | 1 |
| **Outcome Assessment** | 16. Outcome assessment methodology | Medium | Study generally describes that investigators observed mortality and clinical signs at various timepoints during the 14-day observation period. However, details on how those observations were collected were not provided. | 2 | 2 | 4 |
| | 17. Consistency of outcome assessment | Medium | It is inferred that the investigators used the same outcome assessment method for the treated animals based on details provided in the study. However, the study did not address the measures that the investigators put in place to have consistency in the outcome assessment. | 2 | 1 | 2 |
| | 18. Sampling adequacy | High[A] | | 1 | 1 | 1 |
| | 19. Blinding of assessors | Not rated | It is not typically discussed in these studies | NR | NR | NR |
| | 20. Negative Control Response | Not rated | Not rated/applicable - A negative control group was not included. | NR | NR | NR |
| **Confounding/ variable control** | 21. Confounding | Medium | Lack of reporting of food/water intake | 2 | 2 | 4 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | variables in test setup and procedures | | | | | |
| | 22. Outcomes unrelated to exposure | Low | It is not possible to determine if there were confounding variables with the limited information given in the report. | 3 | 1 | 3 |
| **Data presentation and analysis** | 23. Statistical methods | Not rated | Reviewer implied that the investigators did not conduct a statistical analysis. | NR | NR | NR |
| | 24. Reporting of data | Medium | Outcome data were provided. It would have been helpful to have outcome data for the vehicle control. | 2 | 2 | 4 |
| | | | **Sum of scores:** | **42** | **27** | **56** |
| High | Medium | Low | **Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:** | **2.074** | **Overall Score (Rounded):** | **2.1** |
| ≥1 and <1.7 | ≥1.7 and <2.3 | ≥2.3 and ≤3 | **Overall Quality Level:** | | | **Medium** |
| Footnote A: This metric met the criteria for high confidence as expected for this type of study. | | | | | | |

**Table 2. Acute Oral Toxicity Study with Rats, (BASF, 1978d)**

| **Study Reference:** | **BASF. 1978. Study report for CAS 81-33-4, Acute oral toxicity with rats. BASF Report 77/360. [as reported in Translated PV29 Tox Summaries, Product Safety Basel, BASF Schweiz AG, Switzerland, January 31, 2018]. HERO ID: 4731530.** | | | | | |
|---|---|---|---|---|---|---|
| **Note:** | Study guideline was not indicated in the study report | | | | | |
| **Domain** | **Metric** | **Qualitative Determination [*i.e.*, High, Medium, Low, Unacceptable, or Not rated]** | **Comments** | **Metric Score** | **Metric Weighting Factor** | **Weighted Score** |
| **Test Substance** | 1. Test substance identity | Medium | CASRN number was provided (81-33-4) but other expected details were not discussed in the study. For instance, the physical nature of the test substance was not described but it is inferred to be solid state based on the physical/chemical properties of PV29. | 2 | 2 | 4 |
| | 2. Test substance source | Low | No details were provided about the source and lot number of the test substance. | 3 | 1 | 3 |
| | 3.Test substance purity | Low | No details were provided about the test substance purity. | 3 | 1 | 3 |
| **Test setup** | 4. Negative controls | Low | A concurrent negative control group was not reported. It is inferred that the laboratory did not include the negative control because water (vehicle) would not be triggering a response. | 3 | 2 | 6 |
| | 5. Positive controls | Not rated | Not rated/applicable - Positive controls are not necessary for this study type. | NR | NR | NR |
| | 6. Randomized allocation | Low | The study report did not state how animals were allocated to study groups. | 3 | 1 | 3 |
| **Exposure characterization** | 7. Preparation and storage of test substance | Low | Test substance preparation was not fully reported. The vehicle (0.5% aqueous solution of carboxymethylcellulose, 50% suspension with test | 3 | 1 | 3 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | item) was stated, but methods of preparation (*e.g.*, whether methods ensured that test item suspension was homogenous) and storage were not addressed. | | | |
| | 8. Consistency of Exposure administration | Low | Details of exposure administration were not fully reported. The study report states that the test substance was administered as a single gavage application to each animal, but the dosing volume was not reported so it is not evident that exposure administration was the same for all animals. | 3 | 1 | 3 |
| | 9. Reporting of doses / concentrations | High[A] | | 1 | 2 | 2 |
| | 10. Exposure frequency and duration | High[A] | | 1 | 1 | 1 |
| | 11. Number of exposure groups and dose spacing | High[A] | | 1 | 1 | 1 |
| | 12. Exposure route and method | High[A] | | 1 | 1 | 1 |
| **Test organisms** | 13. Test animal characteristics | Medium | Health status and age at initiation were not reported. | 2 | 2 | 4 |
| | 14. Adequacy and consistency of animal husbandry conditions | Low | Study provided minimal information on the adequacy of animal husbandry conditions. | 3 | 1 | 3 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 15. Number per group | High | | 1 | 1 | 1 |
| **Outcome Assessment** | 16. Outcome assessment methodology | Medium | Study generally describes that investigators observed mortality and clinical signs at various timepoints during the 14-day observation period. However, details on how those observations were collected were not provided. | 2 | 2 | 4 |
| | 17. Consistency of outcome assessment | Medium | It is inferred that the investigators used the same outcome assessment method for the treated animals based on details provided in the study. However, the study did not address the measures that the investigators put in place to have consistency in the outcome assessment. | 2 | 1 | 2 |
| | 18. Sampling adequacy | High[A] | | 1 | 1 | 1 |
| | 19. Blinding of assessors | Not rated | It is not typically discussed in these studies. | NR | NR | NR |
| | 20. Negative Control Response | Not rated | Not rated/applicable - A negative control group was not included. | NR | NR | NR |
| **Confounding/ variable control** | 21. Confounding variables in test setup and procedures | Medium | Lack of reporting of food/water intake and respiratory rate | 2 | 2 | 4 |
| | 22. Outcomes unrelated to exposure | Low | It is not possible to determine if there were confounding variables with the limited information given in the report. | 3 | 1 | 3 |
| **Data presentation and analysis** | 23. Statistical methods | Not rated | Reviewer implied that the investigators did not conduct a statistical analysis. | NR | NR | NR |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 24. Reporting of data | Medium | Outcome data were provided. It would have been helpful to have outcome data for the vehicle control. | 2 | 2 | 4 |
| | | | **Sum of scores:** | **42** | **27** | **56** |
| High | Medium | Low | **Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:** | **2.074** | **Overall Score (Rounded):** | **2.1** |
| ≥1 and <1.7 | ≥1.7 and <2.3 | ≥2.3 and ≤3 | **Overall Quality Level:** | | | **Medium** |
| Footnote A: This metric met the criteria for high confidence as expected for this type of study. | | | | | | |

**Table 3. Acute Oral Toxicity Study with Rats, (Rupprich and Weigand, 1984c)**

| Study Reference: | Rupprich, N, Weigand, W. 1984. Testing the acute oral toxicity in the male and female Wistar rat. Hoechst, Pharma Research Toxicology. Report No. 84.0225. Report date: May 2, 1984. HERO ID: 4731531. | | | | | |
|---|---|---|---|---|---|---|
| **Note:** | Study guideline was not indicated in the study report | | | | | |
| **Domain** | **Metric** | **Qualitative Determination [*i.e.*, High, Medium, Low, Unacceptable, or Not rated]** | **Comments** | **Metric Score** | **Metric Weighting Factor** | **Weighted Score** |
| **Test Substance** | 1. Test substance identity | High | The test substance was identified definitively and the specific form was characterized | 1 | 2 | 2 |
| | 2. Test substance source | Medium | Source was incompletely reported. | 2 | 1 | 2 |
| | 3.Test substance purity | Medium | Product contained 80% active ingredient (Perylimid); other components were reported as 10% KOH, 8% diverse organic contaminations, which were not identified, approx 1% inorganic salts, and approx 1% water. | 2 | 1 | 2 |
| **Test setup** | 4. Negative controls | Not rated | A concurrent negative control group is not required for this study type. | NR | NR | NR |
| | 5. Positive controls | Not rated | A concurrent positive control group is not required for this study type. | NR | NR | NR |
| | 6. Randomized allocation | Low | The study did not report how animals were allocated to study groups. | 3 | 1 | 3 |
| **Exposure characterization** | 7. Preparation and storage of test substance | Low | The study report states that the test substance was prepared as a suspension in the | 3 | 1 | 3 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | carrier, 2% starch sludge, but no further details on preparation (*e.g.*, homogeneity of suspension, solubility in starch sludge) or storage of the test substance were reported. | | | |
| | 8. Consistency of Exposure administration | Medium | Consistent dosing volume was reported but, the study report does not specifically state that exposures were otherwise administered consistently (*e.g.*, at the same time of day). | 2 | 1 | 2 |
| | 9. Reporting of doses / concentrations | High[A] | | 1 | 2 | 2 |
| | 10. Exposure frequency and duration | High[A] | | 1 | 1 | 1 |
| | 11. Number of exposure groups and dose spacing | High[A] | | 1 | 1 | 1 |
| | 12. Exposure route and method | High[A] | | 1 | 1 | 1 |
| **Test organisms** | 13. Test animal characteristics | Medium | Health status and age at initiation were not reported. | 2 | 2 | 4 |
| | 14. Adequacy and consistency of animal husbandry conditions | High[A] | | 1 | 1 | 1 |
| | 15. Number per group | High[A] | | 1 | 1 | 1 |
| **Outcome Assessment** | 16. Outcome assessment methodology | High[A] | | 1 | 2 | 2 |
| | 17. Consistency of outcome assessment | High[A] | | 1 | 1 | 1 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 18. Sampling adequacy | High[A] | | 1 | 1 | 1 |
| | 19. Blinding of assessors | Not rated | It is not typically discussed in these studies. | NR | NR | NR |
| | 20. Negative Control Response | Not rated | A negative control group was not included. | NR | NR | NR |
| **Confounding/ variable control** | 21. Confounding variables in test setup and procedures | Medium | Lack of reporting of food/water intake and respiratory rate | 2 | 2 | 4 |
| | 22. Outcomes unrelated to exposure | High[A] | | 1 | 1 | 1 |
| **Data presentation and analysis** | 23. Statistical methods | High | The data was provided, but statistical analysis is not required | 1 | 1 | 1 |
| | 24. Reporting of data | High[A] | | 1 | 2 | 2 |
| | | | **Sum of scores:** | **29** | **26** | **37** |
| High | Medium | Low | **Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:** | **1.423** | **Overall Score (Rounded):** | **1.4** |
| ≥1 and <1.7 | ≥1.7 and <2.3 | ≥2.3 and ≤3 | **Overall Quality Level:** | | | **HIGH** |
| Footnote A: This metric met the criteria for high confidence as expected for this type of study. | | | | | | |

**Table 4. Acute Inhalation Toxicity Study with Rats, (BASF, 1975a)**

| **Study Reference:** | **BASF. 1975. Acute inhalation toxicity with rats. BASF Report XXV/454. Product Safety Basel, BASF Schweiz AG, Switzerland. [as reported in Translated PV29 Tox Summaries, Product Safety Basel, BASF Schweiz AG, Switzerland, January 31, 2018]. HERO ID 4731525.** | | | | | |
|---|---|---|---|---|---|---|
| **Note:** | Study report indicated that this study was not conducted according to a test guideline | | | | | |
| **Domain** | **Metric** | **Qualitative Determination [*i.e.*, High, Medium, Low, Unacceptable, or Not rated]** | **Comments** | **Metric Score** | **Metric Weighting Factor** | **Weighted Score** |
| **Test Substance** | 1. Test substance identity | Medium | CASR number was provided (81-33-4) but other expected details were not discussed in the study. For instance, the physical nature of the test substance was ambiguously characterized mentioning both vapors and dust. | 2 | 2 | 4 |
| | 2. Test substance source | Low | No details were provided about the test substance source. | 3 | 1 | 3 |
| | 3.Test substance purity | Low | No details were provided about the test substance purity. | 3 | 1 | 3 |
| **Test setup** | 4. Negative controls | Medium | The study did not use a vehicle control. The study used a concurrent air control. | 2 | 2 | 4 |
| | 5. Positive controls | Not rated | A positive control is not necessary for this study. | NR | NR | NR |
| | 6. Randomized allocation | Low | The study did not provide details on the randomized | 3 | 1 | 3 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | allocation of animals. | | | |
| **Exposure characterization** | 7. Preparation and storage of test substance | Low | The study did not discuss details about the preparation and/or storage conditions of the test substance. These details are important to determine if the animals were properly exposed to a well-characterized test substance under carefully controlled conditions. | 3 | 1 | 3 |
| | 8. Consistency of Exposure administration | Unacceptable | Reviewer cannot determine whether consistency of exposure was achieved due to lack of analytical method to measure exposure in the chamber (*e.g.*, only nominal concentrations were reported). | **4** | 1 | 4 |
| | 9. Reporting of doses / concentrations | Unacceptable | Nominal but not actual concentrations were reported. Nominal concentrations are usually quite close to actual concentrations for gases, but they can be much greater for vapor and aerosols. This creates a major uncertainty in the study. | **4** | 2 | 8 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 10. Exposure frequency and duration | Low | Rats were exposed in an atmosphere saturated with vapors for 8 hrs. The exposure duration is not typical for an acute inhalation study and this was not explained. | 3 | 1 | 3 |
| | 11. Number of exposure groups and dose spacing | Low | Air control and one exposure concentration were conducted. The objective of the test was not described which would have helped to understand if a single test concentration or multiple concentrations would be appropriate. | 3 | 1 | 3 |
| | 12. Exposure route and method | Unacceptable | The study aimed at investigating animal toxicity to an atmosphere saturated with vapors of the volatile component of PV29. Since the study said that dust is expected by inhalation, this is an inappropriate exposure method. Further, specific details were missing such as the equipment and method used to generate the | **4** | 1 | 4 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | chamber atmosphere, description of the inhalation chamber, failure to use an analytical method to analyze the test atmosphere concentrations. Also, the authors admitted the limitations of the study by indicating that "the inhalation hazard test is insufficient for non-volatile substances". | | | |
| **Test organisms** | 13. Test animal characteristics | Low | Study provided minimal information on the test animal characteristics (*e.g.*, strain, health status, age). | 3 | 2 | 6 |
| | 14. Adequacy and consistency of animal husbandry conditions | Low | Study provided minimal information on the adequacy of animal husbandry conditions. | 3 | 1 | 3 |
| | 15. Number per group | Medium | Number of animals per treatment group/sex was considered adequate for an acute inhalation study. There were observed variations in the number of animals for air control groups (3 rats/sex) and treatment group (6 rats/sex), but no explanation was offered to | 2 | 1 | 2 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | account for the difference. | | | |
| **Outcome Assessment** | 16. Outcome assessment methodology | Low | Significant deficiencies in the reported outcome assessment methodology (*i.e.*, limited information available). | 3 | 2 | 6 |
| | 17. Consistency of outcome assessment | Low | Details regarding the execution of the study protocol for outcome assessment (*e.g.*, timing of assessment across groups) were not discussed. | 3 | 1 | 3 |
| | 18. Sampling adequacy | Medium | Details regarding sampling of outcomes were not reported. Mortality incidence was recorded in the data table at five exposure times (3 min, 10 min, 1 hr, 3 hrs and 8 hrs). The reviewer implied that the investigators assessed mortality and clinical signs frequently during the 8-hr exposure, but this was not explicitly explained in the report. Rats were observed for 7 days after cessation of exposure. | 2 | 1 | 2 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 19. Blinding of assessors | Not rated | Blinding is not typically done for acute inhalation studies that are assessing mortality, clinical signs (*e.g.*, irritation) and gross pathology. | NR | NR | NR |
| | 20. Negative Control Response | Low | The biological responses of the negative control group(s) were reported, but the responses for the negative controls have high uncertainties due to the exposure characterization issues in the study. | 3 | 1 | 3 |
| **Confounding/ variable control** | 21. Confounding variables in test setup and procedures | Low | Although initial body weight was reported, the post-treatment body weights were not reported to confirm the study's claim that the treatment did not affect body weight. It is not possible to determine if there were confounding variables with the limited information given in the report. | 3 | 2 | 6 |
| | 22. Outcomes unrelated to exposure | Low | It is not possible to determine whether health outcomes unrelated to exposure | 3 | 1 | 3 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | affected reported outcomes given the limited information in the report. | | | |
| **Data presentation and analysis** | 23. Statistical methods | Not rated | Reviewer implied that the investigators did not conduct a statistical analysis because it was not necessary (*e.g.*, one control group, one treatment group, no effects observed). | NR | NR | NR |
| | 24. Reporting of data | Low | Outcome data were minimally provided and discussed. | 3 | 2 | 6 |
| | | | **Sum of scores:** | | **28** | **82** |
| High | Medium | Low | **Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:** | 2.929 | **Overall Score (Rounded):** | **2.9** [1] |
| ≥1 and <1.7 | ≥1.7 and <2.3 | ≥2.3 and ≤3 | **Overall Quality Level:** | | | **Unacceptable**[1] |

Footnote 1: Consistent with our Application of Systematic Review in TSCA Risk Evaluations document, if a metric for a data source receives a score of Unacceptable (score = 4), EPA will determine the study to be unacceptable. In this case, three of the metrics were rated as unacceptable. As such, the study is considered unacceptable and the score is presented solely to increase transparency.

**Table 5. Acute Inhalation Toxicity Study with Rats, (BASF, 1978b)**

| **Study Reference:** | **BASF. 1978. Study report for CAS 81-33-4, Acute inhalation toxicity with rats. BASF Report 77/360. [as reported in Translated PV29 Tox Summaries, Product Safety Basel, BASF Schweiz AG, Switzerland, January 31, 2018]. HERO ID: 4731526.** | | | | | |
|---|---|---|---|---|---|---|
| **Note:** | Study report indicated that this study was not conducted according to a test guideline | | | | | |
| **Domain** | **Metric** | **Qualitative Determination [*i.e.*, High, Medium, Low, Unacceptable, or Not rated]** | **Comments** | **Metric Score** | **Metric Weighting Factor** | **Weighted Score** |
| **Test Substance** | 1. Test substance identity | Medium | CASR number was provided (81-33-4) but other expected details were not discussed in the study. For instance, the physical nature of the test substance was ambiguously characterized mentioning both vapors and dust. | 2 | 2 | 4 |
| | 2. Test substance source | Low | No details were provided about the test substance source. | 3 | 1 | 3 |
| | 3.Test substance purity | Low | No details were provided about the test substance purity. | 3 | 1 | 3 |
| **Test setup** | 4. Negative controls | Unacceptable | The study did not use a vehicle control. The study used a concurrent air control. | **4** | 2 | 8 |
| | 5. Positive controls | Not rated | A positive control is not necessary for this study. | NR | NR | NR |
| | 6. Randomized allocation | Low | The study did not provide details on the randomized allocation of animals. | 3 | 1 | 3 |
| **Exposure characterization** | 7. Preparation and storage of test substance | Low | The study did not discuss details about the preparation and/or storage conditions of the test substance. These | 3 | 1 | 3 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | details are important to determine if the animals were properly exposed to a well-characterized test substance under carefully controlled conditions. | | | |
| | 8. Consistency of Exposure administration | Unacceptable | Reviewer cannot determine whether consistency of exposure was achieved due to lack of analytical method to measure exposure in the chamber (*e.g.*, only nominal concentrations were reported). | **4** | 1 | 4 |
| | 9. Reporting of doses / concentrations | Unacceptable | Nominal but not actual concentrations were reported. Nominal concentrations are usually quite close to actual concentrations for gases, but they can be much greater for vapor and aerosols. This creates a major uncertainty in the study. | **4** | 2 | 8 |
| | 10. Exposure frequency and duration | Low | Rats were exposed in an atmosphere saturated with vapors for 7 hrs. The exposure duration is not typical for an acute inhalation study and this was not explained. | 3 | 1 | 3 |
| | 11. Number of exposure groups and dose spacing | Low | Study included one exposure concentration but no mention about the air control groups. The | 3 | 1 | 3 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | objective of the test was not described which would have helped to understand if a single test concentration or multiple concentrations would be appropriate. | | | |
| | 12. Exposure route and method | Unacceptable | The study aimed at investigating animal toxicity to an atmosphere saturated with vapors of the volatile component of PV29. Since the study said that dust is expected by inhalation, this is an inappropriate exposure method. Further, specific details were missing such as the equipment and method used to generate the chamber atmosphere, description of the inhalation chamber, failure to use an analytical method to analyze the test atmosphere concentrations. Also, the authors admitted the limitations of the study by indicating that “the inhalation hazard test is insufficient for non-volatile substances”. | **4** | 1 | 4 |
| **Test organisms** | 13. Test animal characteristics | Low | Study provided minimal information on the test animal characteristics | 3 | 2 | 6 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | (*e.g.*, strain, health status, age). | | | |
| | 14. Adequacy and consistency of animal husbandry conditions | Low | Study provided minimal information on the adequacy of animal husbandry conditions. | 3 | 1 | 3 |
| | 15. Number per group | Low | Number of animals per treatment group/sex was considered adequate for an acute inhalation study. Report did not report the number of animals for air control groups. Reviewer assumed that the investigators might have used the air control groups from the previous 8-hr acute inhalation toxicity study. | 3 | 1 | 3 |
| **Outcome Assessment** | 16. Outcome assessment methodology | Low | Significant deficiencies in the reported outcome assessment methodology (*i.e.*, limited information available). | 3 | 2 | 6 |
| | 17. Consistency of outcome assessment | Low | Details regarding the execution of the study protocol for outcome assessment (*e.g.*, timing of assessment across groups) were not discussed. | 3 | 1 | 3 |
| | 18. Sampling adequacy | Medium | Details regarding sampling of outcomes were not reported. Mortality incidence was recorded in the data table at five exposure times (3 min, 10 min, 1 hr, 3 hrs and 7 hrs). | 2 | 1 | 2 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | The reviewer implied that the investigators assessed mortality and clinical signs frequently during the 8-hr exposure, but this was not explicitly explained in the report. Rats were observed for 7 days after cessation of exposure. | | | |
| | 19. Blinding of assessors | Not rated | Blinding is not typically done for acute inhalation studies that are assessing mortality, clinical signs (*e.g.*, irritation) and gross pathology. | NR | NR | NR |
| | 20. Negative Control Response | Unacceptable | The biological responses of the negative control group(s) were not addressed in the study. | **4** | 1 | 4 |
| **Confounding/ variable control** | 21. Confounding variables in test setup and procedures | Low | Although initial body weight was reported, the post-treatment body weights were not reported to confirm the study's claim that the treatment did not affect body weight. It is not possible to determine if there were confounding variables with the limited information given in the report. | 3 | 2 | 6 |
| | 22. Outcomes unrelated to exposure | Low | It is not possible to determine whether health outcomes unrelated to exposure affected reported outcomes given the limited | 3 | 1 | 3 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | information in the report. | | | |
| **Data presentation and analysis** | 23. Statistical methods | Not rated | Reviewer implied that the investigators did not conduct a statistical analysis because it was not necessary (*e.g.*, one control group, one treatment group, no effects observed). | NR | NR | NR |
| | 24. Reporting of data | Unacceptable | Data presentation was inadequate (*e.g.*, the report does not differentiate among findings between air control and treatment groups). | **4** | 2 | 8 |
| | | | **Sum of scores:** | | **28** | **90** |
| High | Medium | Low | **Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:** | **3.214** | **Overall Score (Rounded):** | **3.2** [1] |
| ≥1 and <1.7 | ≥1.7 and <2.3 | ≥2.3 and ≤3 | **Overall Quality Level:** | | | **Unacceptable**[1] |

Footnote 1: Consistent with our Application of Systematic Review in TSCA Risk Evaluations document, if a metric for a data source receives a score of Unacceptable (score = 4), EPA will determine the study to be unacceptable. In this case, seven of the metrics were rated as unacceptable. As such, the study is considered unacceptable and the score is presented solely to increase transparency.

**Table 6. Acute Intraperitoneal Toxicity Study with Mice, (BASF, 1975e)**

| Study Reference: | BASF. 1975. Summary of toxicological investigations with CAS 81-33-4, Acute intraperitoneal toxicity with mice. BASF Report XXV/454. [as reported in Translated PV29 Tox Summaries, Product Safety Basel, BASF Schweiz AG, Switzerland, January 31, 2018]. HERO ID: 4731527. | | | | | |
|---|---|---|---|---|---|---|
| **Note:** | Study report indicated that this study was not conducted according to a test guideline but was conducted according to an internal protocol. | | | | | |
| **Domain** | **Metric** | **Qualitative Determination [*i.e.*, High, Medium, Low, Unacceptable, or Not rated]** | **Comments** | **Metric Score** | **Metric Weighting Factor** | **Weighted Score** |
| **Test Substance** | 1. Test substance identity | Medium | CASRN number was provided (81-33-4) but other expected details were not discussed in the study. For instance, the physical nature of the test substance was not described but it is inferred to be solid state based on the physical/chemical properties of PV29. | 2 | 2 | 4 |
| | 2. Test substance source | Low | No details were provided about the source and lot number of the test substance. | 3 | 1 | 3 |
| | 3.Test substance purity | Low | No details were provided about the test substance purity. | 3 | 1 | 3 |
| **Test setup** | 4. Negative controls | Low | A concurrent negative control group was not reported. It is inferred that the laboratory had historical data testing mice with carboxymethyl cellulose (vehicle) and showing no mortality. Carboxymethyl cellulose is non-toxic. | 3 | 2 | 6 |
| | 5. Positive controls | Not rated | Not rated/applicable - A concurrent positive control group is not required for this study type. | NR | NR | NR |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 6. Randomized allocation | Low | The study report did not state how animals were allocated to study groups. | 3 | 1 | 3 |
| **Exposure characterization** | 7. Preparation and storage of test substance | Low | Test substance preparation was not fully reported. The vehicle (0.5% aqueous carboxylmethyl cellulose, 21.5%, 46.4% or 50% aqueous suspension) was stated, but the methods of preparation (*e.g.*, whether methods ensured that test item suspension was homogenous) and storage were not addressed. | 3 | 1 | 3 |
| | 8. Consistency of Exposure administration | Low | Details of exposure administration were not fully reported. The study report states that the test substance was administered as a single intraperitoneal application but the volume administered was not reported. | 3 | 1 | 3 |
| | 9. Reporting of doses / concentrations | High[A] | | 1 | 2 | 2 |
| | 10. Exposure frequency and duration | High | Single I.P injection | 1 | 1 | 1 |
| | 11. Number of exposure groups and dose spacing | High | 3 exposure groups | 1 | 1 | 1 |
| | 12. Exposure route and method | High[A] | | 1 | 1 | 1 |
| **Test organisms** | 13. Test animal characteristics | Low | Study provided minimal information on the test animal characteristics (*e.g.*, strain, health status, age). | 3 | 2 | 6 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 14. Adequacy and consistency of animal husbandry conditions | Low | Study provided minimal information on the adequacy of animal husbandry conditions. | 3 | 1 | 3 |
| | 15. Number per group | High | 5 animals per sex per exposure group | 1 | 1 | 1 |
| **Outcome Assessment** | 16. Outcome assessment methodology | Medium | Study generally describes that investigators observed mortality and clinical signs at various timepoints during the 14-day observation period. However, details on how those observations were collected were not provided. | 2 | 2 | 4 |
| | 17. Consistency of outcome assessment | Low | Details regarding the execution of the study protocol for outcome assessment (*e.g.*, timing of assessment across groups) were not reported, and these deficiencies are likely to have a substantial impact on results. | 3 | 1 | 3 |
| | 18. Sampling adequacy | High[A] | | 1 | 1 | 1 |
| | 19. Blinding of assessors | Not rated | It is not typically discussed in these studies. | NR | NR | NR |
| | 20. Negative Control Response | Not rated | Not rated/applicable - A negative control group was not included. | NR | NR | NR |
| **Confounding/ variable control** | 21. Confounding variables in test setup and procedures | Low | Although initial body weight was reported, the post-treatment body weights were not reported to confirm the study's claim that the treatment did not affect body weight. It is not possible to determine if there were | 3 | 2 | 6 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | confounding variables with the limited information given in the report. | | | |
| | 22. Outcomes unrelated to exposure | Low | It is not possible to determine if there were confounding variables with the limited information given in the report. | 3 | 1 | 3 |
| **Data presentation and analysis** | 23. Statistical methods | Not rated | Reviewer implied that the investigators did not conduct a statistical analysis. | NR | NR | NR |
| | 24. Reporting of data | Low | Outcome data were minimally provided and discussed. | 3 | 2 | 6 |
| | | | **Overall Score:** | **46** | **27** | **63** |
| High | Medium | Low | **Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:** | **2.333** | **Overall Score (Rounded):** | **2.3** |
| ≥1 and <1.7 | ≥1.7 and <2.3 | ≥2.3 and ≤3 | **Overall Quality Level:** | | | **Low** |
| Footnote A: This metric met the criteria for high confidence as expected for this type of study. | | | | | | |

**Table 7. Acute Intraperitoneal Toxicity Study with Mice, (BASF, 1978c)**

| Study Reference: | BASF. 1978. Study report for CAS 81-33-4, Acute intraperitoneal toxicity with mice. BASF Report 77/360. [as reported in Translated PV29 Tox Summaries, Product Safety Basel, BASF Schweiz AG, Switzerland, January 31, 2018]. HERO ID: 4731528. | | | | | |
|---|---|---|---|---|---|---|
| **Note:** | Study report indicated that this study was not conducted according to a test guideline but was conducted according to an internal protocol. | | | | | |
| **Domain** | **Metric** | **Qualitative Determination [*i.e.*, High, Medium, Low, Unacceptable, or Not rated]** | **Comments** | **Metric Score** | **Metric Weighting Factor** | **Weighted Score** |
| **Test Substance** | 1. Test substance identity | Medium | CASRN number was provided (81-33-4) but other expected details were not discussed in the study. For instance, the physical nature of the test substance was not described but it is inferred to be solid state based on the physical/chemical properties of PV29. | 2 | 2 | 4 |
| | 2. Test substance source | Low | No details were provided about the source and lot number of the test substance. | 3 | 1 | 3 |
| | 3.Test substance purity | Low | No details were provided about the test substance purity. | 3 | 1 | 3 |
| **Test setup** | 4. Negative controls | Low | A concurrent negative control group was not reported. It is inferred that the laboratory had historical data testing mice with carboxymethyl cellulose (vehicle) and showing no mortality. Carboxymethyl cellulose is non-toxic. | 3 | 2 | 6 |
| | 5. Positive controls | Not rated | Not rated/applicable - A concurrent positive control group is not required for this study type. | NR | NR | NR |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 6. Randomized allocation | Low | The study report did not state how animals were allocated to study groups. | 3 | 1 | 3 |
| **Exposure characterization** | 7. Preparation and storage of test substance | Low | Test substance preparation was not fully reported. The vehicle (0.5% aqueous carboxylmethyl cellulose, 46.4% or 50% aqueous suspension) was stated, but the methods of preparation (*e.g.*, whether methods ensured that test item suspension was homogenous) and storage were not addressed. | 3 | 1 | 3 |
| | 8. Consistency of Exposure administration | Low | Details of exposure administration were not fully reported. The study report states that the test substance was administered as a single intraperitoneal application but the volume administered was not reported. | 3 | 1 | 3 |
| | 9. Reporting of doses / concentrations | High[A] | | 1 | 2 | 2 |
| | 10. Exposure frequency and duration | High | Single I.P injection | 1 | 1 | 1 |
| | 11. Number of exposure groups and dose spacing | High | 3 exposure groups | 1 | 1 | 1 |
| | 12. Exposure route and method | High[A] | | 1 | 1 | 1 |
| **Test organisms** | 13. Test animal characteristics | Low | Study provided minimal information on the test animal characteristics (*e.g.*, strain, health status, age). | 3 | 2 | 6 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 14. Adequacy and consistency of animal husbandry conditions | Low | Study provided minimal information on the adequacy of animal husbandry conditions. | 3 | 1 | 3 |
| | 15. Number per group | High | 5 animals per sex per exposure group | 1 | 1 | 1 |
| **Outcome Assessment** | 16. Outcome assessment methodology | Medium | Study generally describes that investigators observed mortality and clinical signs at various timepoints during the 14-day observation period. However, details on how those observations were collected were not provided. | 2 | 2 | 4 |
| | 17. Consistency of outcome assessment | Low | Details regarding the execution of the study protocol for outcome assessment (*e.g.*, timing of assessment across groups) were not reported, and these deficiencies are likely to have a substantial impact on results. | 3 | 1 | 3 |
| | 18. Sampling adequacy | High[A] | | 1 | 1 | 1 |
| | 19. Blinding of assessors | Not rated | It is not typically discussed in these studies. | NR | NR | NR |
| | 20. Negative Control Response | Not rated | Not rated/applicable - A negative control group was not included. | NR | NR | NR |
| **Confounding/ variable control** | 21. Confounding variables in test setup and procedures | Low | Although initial body weight was reported, the post-treatment body weights were not reported to confirm the study's claim that the treatment did not affect body weight. It is not possible to determine if there were confounding | 3 | 2 | 6 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | variables with the limited information given in the report. | | | |
| | 22. Outcomes unrelated to exposure | Low | It is not possible to determine if there were confounding variables with the limited information given in the report. | 3 | 1 | 3 |
| **Data presentation and analysis** | 23. Statistical methods | Not rated | Reviewer implied that the investigators did not conduct a statistical analysis. | NR | NR | NR |
| | 24. Reporting of data | Medium | Outcome data were provided. It would have been helpful to have outcome data for the vehicle control. | 2 | 2 | 4 |
| | | | **Overall Score:** | **45** | **27** | **61** |
| High | Medium | Low | **Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:** | **2.259** | **Overall Score (Rounded):** | **2.3** |
| ≥1 and <1.7 | ≥1.7 and <2.3 | ≥2.3 and ≤3 | **Overall Quality Level:** | | | **Low** |
| Footnote A: This metric met the criteria for high confidence as expected for this type of study. | | | | | | |

**Table 8. Reproduction/Developmental Toxicity Screening Test with Rats, (Stark et al., 2013)**

| Study Reference: | Stark, D., Treumann, S., van Ravenzwaay, B. 2013. Reproduction/developmental Toxicity Screening Test with Wistar Rats Oral Administration (Gavage). BASF SE, Germany. Project No. 80R0223/11C162. For BASF SE, Germany. HERO ID: 4731538. | | | | | |
|---|---|---|---|---|---|---|
| **Note:** | Study report indicates the study was conducted according to OECD TG 421 and OPPTS 870.3550 | | | | | |
| **Domain** | **Metric** | **Qualitative Determination [*i.e.*, High, Medium, Low, Unacceptable, or Not rated]** | **Comments** | **Metric Score** | **Metric Weighting Factor** | **Weighted Score** |
| **Test Substance** | 1. Test substance identity | High | The test substance was identified definitively and detailed analysis of the characterization including a description of the form was provided. | 1 | 2 | 2 |
| | 2. Test substance source | High | Test item was received by the submitter and the batch number was provided. | 1 | 1 | 1 |
| | 3.Test substance purity | High | Purity was characterized in the appendix of the study. | 1 | 1 | 1 |
| **Test setup** | 4. Negative controls | High[A] | | 1 | 2 | 2 |
| | 5. Positive controls | Not rated | No positive controls were needed for this study. | NR | NR | NR |
| | 6. Randomized allocation | Medium | Animals were distributed according to weight so that weight variations did not exceed 20% of the mean weight of each sex. | 2 | 1 | 2 |
| **Exposure characterization** | 7. Preparation and storage of test substance | High[A] | | 1 | 1 | 1 |
| | 8. Consistency of Exposure administration | High[A] | | 1 | 1 | 1 |
| | 9. Reporting of doses / concentrations | High[A] | | 1 | 2 | 2 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 10. Exposure frequency and duration | High[A] | | 1 | 1 | 1 |
| | 11. Number of exposure groups and dose spacing | High[A] | | 1 | 1 | 1 |
| | 12. Exposure route and method | High[A] | | 1 | 1 | 1 |
| **Test organisms** | 13. Test animal characteristics | High[A] | | 1 | 2 | 2 |
| | 14. Adequacy and consistency of animal husbandry conditions | High[A] | | 1 | 1 | 1 |
| | 15. Number per group | High[A] | | 1 | 1 | 1 |
| **Outcome Assessment** | 16. Outcome assessment methodology | High[A] | | 1 | 2 | 2 |
| | 17. Consistency of outcome assessment | High[A] | | 1 | 1 | 1 |
| | 18. Sampling adequacy | High[A] | | 1 | 1 | 1 |
| | 19. Blinding of assessors | Not rated | Initial histopathology review was the only subjective assessment conducted, and this metric is not applicable. | NR | NR | NR |
| | 20. Negative Control Response | High[A] | | 1 | 1 | 1 |
| **Confounding/ variable control** | 21. Confounding variables in test setup and procedures | High[A] | | 1 | 2 | 2 |
| | 22. Outcomes unrelated to exposure | High[A] | | 1 | 1 | 1 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Data presentation and analysis** | 23. Statistical methods | High[A] | | 1 | 1 | 1 |
| | 24. Reporting of data | High[A] | | 1 | 2 | 2 |
| | | | **Sum of scores:** | **23** | **29** | **30** |
| High | Medium | Low | **Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:** | **1.034** | **Overall Score (Rounded):** | **1.0** |
| ≥1 and <1.7 | ≥1.7 and <2.3 | ≥2.3 and ≤3 | **Overall Quality Level:** | | | **HIGH** |
| Footnote A: This metric met the criteria for high confidence as expected for this type of study. | | | | | | |

**Table 9. Acute Dermal Irritation Study, (BASF, 1975d)**

| Study Reference: | BASF. 1975. Skin irritation study. BASF Report XXV/454. Product Safety Basel, BASF Schweiz AG, Switzerland. [as reported in Translated PV29 Tox Summaries, Product Safety Basel, BASF Schweiz AG, Switzerland, January 31, 2018]. HERO ID: 4731532. | | | | | |
|---|---|---|---|---|---|---|
| **Note:** | Study guideline was not indicated in the study report | | | | | |
| **Domain** | **Metric** | **Qualitative Determination [*i.e.*, High, Medium, Low, Unacceptable, or Not rated]** | **Comments** | **Metric Score** | **Metric Weighting Factor** | **Weighted Score** |
| **Test Substance** | 1. Test substance identity | Medium | CASRN number was provided (81-33-4) but other expected details were not discussed in the study. For instance, the physical nature of the test substance was not described but it is inferred to be solid state based on the physical/chemical properties of PV29. | 2 | 2 | 4 |
| | 2. Test substance source | Low | No details were provided about the source and lot number of the test substance. | 3 | 1 | 3 |
| | 3.Test substance purity | Low | No details were provided about the test substance purity. | 3 | 1 | 3 |
| **Test setup** | 4. Negative controls | Medium | Use of a negative control was not reported, but this is not considered to have a substantial impact on results since untreated skin usually serves as the negative control in this type of study. | 2 | 2 | 4 |
| | 5. Positive controls | Not rated | Positive controls are typically not necessary for this study type. | NR | NR | NR |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 6. Randomized allocation | Not rated | Only two individual animals were tested, so randomization was not required. | NR | NR | NR |
| **Exposure characterization** | 7. Preparation and storage of test substance | Low | The study report states that the test substance was prepared as a 50% aqueous suspension in water; however, no details were provided on test substance preparation (*e.g.*, stirring, and whether homogenous when applied). | 3 | 1 | 3 |
| | 8. Consistency of Exposure administration | Low | Few details were provided on application of the test substance to skin so it is not clear that exposures were consistent. | 3 | 1 | 3 |
| | 9. Reporting of doses / concentrations | Low | Study report states that test substance was given as a 50% aqueous suspension, but no details are provided on the actual amount (*e.g.*, grams) of test substance administered in the application. | 3 | 2 | 6 |
| | 10. Exposure frequency and duration | High[A] | | 1 | 1 | 1 |
| | 11. Number of exposure groups and dose spacing | High[A] | | 1 | 1 | 1 |
| | 12. Exposure route and method | High[A] | | 1 | 1 | 1 |
| **Test organisms** | 13. Test animal characteristics | Medium | Health status and age at initiation of treatment were not reported. | 2 | 2 | 4 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 14. Adequacy and consistency of animal husbandry conditions | Low | Study provided minimal information on the adequacy of animal husbandry conditions. | 3 | 1 | 3 |
| | 15. Number per group | Low | Only two animals were treated. | 3 | 1 | 3 |
| **Outcome Assessment** | 16. Outcome assessment methodology | Low | Significant deficiencies in the reported outcome assessment methodology (*i.e.*, limited information). | 3 | 2 | 6 |
| | 17. Consistency of outcome assessment | High[A] | | 1 | 1 | 1 |
| | 18. Sampling adequacy | High[A] | | 1 | 1 | 1 |
| | 19. Blinding of assessors | Not rated | It is not typically discussed in these studies. Note that the grading of dermal responses is subjective. Training in observing the dermal responses and translating them to a score promotes harmonization of subjective results. | NR | NR | NR |
| | 20. Negative Control Response | Not rated | Negative controls were not required for the study. | NR | NR | NR |
| **Confounding/ variable control** | 21. Confounding variables in test setup and procedures | Medium | Initial food/water intake were not reported but this is not likely to have a significant impact on results. | 2 | 2 | 4 |
| | 22. Outcomes unrelated to exposure | Low | It is not possible to determine if there were confounding variables with the limited information given in the report. | 3 | 1 | 3 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Data presentation and analysis** | 23. Statistical methods | Not rated | Reviewer implied that the investigators did not conduct a statistical analysis. | NR | NR | NR |
| | 24. Reporting of data | High | Dermal responses were reported for both female rabbits at different timepoints. | 1 | 2 | 2 |
| | | | **Sum of scores:** | 41 | **26** | **56** |
| High | Medium | Low | **Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:** | **2.154** | **Overall Score (Rounded):** | **2.2** |
| ≥1 and <1.7 | ≥1.7 and <2.3 | ≥2.3 and ≤3 | **Overall Quality Level:** | | | **Medium** |
| Footnote A: This metric met the criteria for high confidence as expected for this type of study. | | | | | | |

**Table 10. Acute Dermal Irritation Study, (BASF, 1978e)**

| Study Reference: | BASF. 1978. Study report for CAS 81-33-4, Skin irritation study. BASF Report 77/360. [as reported in Translated PV29 Tox Summaries, Product Safety Basel, BASF Schweiz AG, Switzerland, January 31, 2018]. HERO ID: 4731533. | | | | | |
|---|---|---|---|---|---|---|
| **Note:** | Study report did not indicate whether a test guideline was followed. | | | | | |
| **Domain** | **Metric** | **Qualitative Determination [*i.e.*, High, Medium, Low, Unacceptable, or Not rated]** | **Comments** | **Metric Score** | **Metric Weighting Factor** | **Weighted Score** |
| **Test Substance** | 1. Test substance identity | Medium | CASRN number was provided (81-33-4) but other expected details were not discussed in the study. For instance, the physical nature of the test substance was not described but it is inferred to be solid state based on the physical/chemical properties of PV29. | 2 | 2 | 4 |
| | 2. Test substance source | Low | No details were provided about the source and lot number of the test substance. | 3 | 1 | 3 |
| | 3.Test substance purity | Low | No details were provided about the test substance purity. | 3 | 1 | 3 |
| **Test setup** | 4. Negative controls | Medium | Use of a negative control was not reported, but this is not considered to have a substantial impact on results since untreated skin usually serves as the negative control in this type of study. | 2 | 2 | 4 |
| | 5. Positive controls | Not rated | Positive controls are typically not necessary for this study type. | NR | NR | NR |
| | 6. Randomized allocation | Not rated | Only two individual animals were tested, so | NR | NR | NR |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | randomization was not required. | | | |
| **Exposure characterization** | 7. Preparation and storage of test substance | Low | The study report states that the test substance was prepared as a 50% aqueous suspension in water; however, no details were provided on test substance preparation (*e.g.*, stirring, and whether homogenous when applied). | 3 | 1 | 3 |
| | 8. Consistency of Exposure administration | Low | Few details were provided on application of the test substance to skin so it is not clear that exposures were consistent. | 3 | 1 | 3 |
| | 9. Reporting of doses / concentrations | Low | Study report states that test substance was given as a 50% aqueous suspension, but no details are provided on the actual amount (*e.g.*, grams) of test substance administered in the application. | 3 | 2 | 6 |
| | 10. Exposure frequency and duration | High[A] | | 1 | 1 | 1 |
| | 11. Number of exposure groups and dose spacing | High[A] | | 1 | 1 | 1 |
| | 12. Exposure route and method | High[A] | | 1 | 1 | 1 |
| **Test organisms** | 13. Test animal characteristics | High | Health status and age at initiation of treatment were not reported. | 1 | 2 | 2 |
| | 14. Adequacy and consistency of animal | Medium | Study provided minimal information on the adequacy of animal | 2 | 1 | 2 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | husbandry conditions | | husbandry conditions. | | | |
| | 15. Number per group | Low | Only three animals were treated. | 3 | 1 | 3 |
| **Outcome Assessment** | 16. Outcome assessment methodology | Low | Significant deficiencies in the reported outcome assessment methodology (*i.e.*, limited information). | 3 | 2 | 6 |
| | 17. Consistency of outcome assessment | High[A] | | 1 | 1 | 1 |
| | 18. Sampling adequacy | High[A] | | 1 | 1 | 1 |
| | 19. Blinding of assessors | Not rated | It is not typically done. Note that the grading of dermal responses is subjective. Training in observing the dermal responses and translating them to a score promotes harmonization of subjective results. | NR | NR | NR |
| | 20. Negative Control Response | Not rated | Negative controls were not required for the study. | NR | NR | NR |
| **Confounding/ variable control** | 21. Confounding variables in test setup and procedures | Medium | Initial food/water intake were not reported but this is not likely to have a significant impact on results. | 2 | 2 | 4 |
| | 22. Outcomes unrelated to exposure | Low | It is not possible to determine if there were confounding variables with the limited information given in the report. | 3 | 1 | 3 |
| **Data presentation and analysis** | 23. Statistical methods | Not rated | Reviewer implied that the investigators did not conduct a statistical analysis. | NR | NR | NR |
| | 24. Reporting of data | High | Dermal responses were reported for male and female | 1 | 2 | 2 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | rabbits at different timepoints. | | | |
| | | | **Sum of scores:** | **39** | **26** | **53** |
| High | Medium | Low | **Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:** | **2.038** | **Overall Score (Rounded):** | **2.0** |
| ≥1 and <1.7 | ≥1.7 and <2.3 | ≥2.3 and ≤3 | **Overall Quality Level:** | | | **Medium** |
| Footnote A: This metric met the criteria for high confidence as expected for this type of study. | | | | | | |

**Table 11. Acute Dermal Irritation Study, (Rupprich and Weigand, 1984a)**

| Study Reference: | Rupprich, N., Weigand, W. 1984. Perylimid Testing the acute dermal irritant effects/caustic effects on the rabbit eye. Hoechst Pharma Research Toxicology, Germany. Report No. 84.0228. For Farben Nord, Werk Höchst. HERO ID: 4731534 | | | | | |
|---|---|---|---|---|---|---|
| **Note:** | Study was conducted according to OECD TG 404 Acute Dermal Irritation / Corrosion (1981). | | | | | |
| **Domain** | **Metric** | **Qualitative Determination [*i.e.*, High, Medium, Low, Unacceptable, or Not rated]** | **Comments** | **Metric Score** | **Metric Weighting Factor** | **Weighted Score** |
| **Test Substance** | 1. Test substance identity | High | The test substance was identified definitively and the specific form was characterized | 1 | 2 | 2 |
| | 2. Test substance source | Medium | No details were provided about the source and lot number of the test substance. | 2 | 1 | 2 |
| | 3.Test substance purity | Medium | Product contained 80% active ingredient (Perylimid); other components were reported as 10% KOH, 8% diverse organic contaminations, which were not identified, approx 1% inorganic salts, and approx 1% water. | 2 | 1 | 2 |
| **Test setup** | 4. Negative controls | Not rated | In acute dermal studies, negative controls are not generally used. | NR | NR | NR |
| | 5. Positive controls | Not rated | Positive controls not required for the study. | NR | NR | NR |
| | 6. Randomized allocation | Not rated | Only one group was included, so randomization was not required. | NR | NR | NR |
| **Exposure characterization** | 7. Preparation and storage of test substance | Low | Amount applied was given but the storage and solubility was not given. 500mg may not dissolve in | 3 | 1 | 3 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | 0.3ml of 0.9% NaCl solution. | | | |
| | 8. Consistency of Exposure administration | High[A] | | 1 | 1 | 1 |
| | 9. Reporting of doses / concentrations | High | 500mg was applied in 0.3ml of 0.9% NaCl solution | 1 | 2 | 2 |
| | 10. Exposure frequency and duration | High[A] | | 1 | 1 | 1 |
| | 11. Number of exposure groups and dose spacing | High[A] | | 1 | 1 | 1 |
| | 12. Exposure route and method | High[A] | | 1 | 1 | 1 |
| **Test organisms** | 13. Test animal characteristics | Medium | Details were not reported including age and sex. | 2 | 2 | 4 |
| | 14. Adequacy and consistency of animal husbandry conditions | High | Husbandry conditions were reported | 1 | 1 | 1 |
| | 15. Number per group | High[A] | | 1 | 1 | 1 |
| **Outcome Assessment** | 16. Outcome assessment methodology | High[A] | | 1 | 2 | 2 |
| | 17. Consistency of outcome assessment | High[A] | | 1 | 1 | 1 |
| | 18. Sampling adequacy | High[A] | | 1 | 1 | 1 |
| | 19. Blinding of assessors | Not rated | It is not typically discussed in these studies. Note that the grading of dermal responses is subjective. Training in observing the dermal responses and translating them to a score promotes | NR | NR | NR |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | harmonization of subjective results. | | | |
| | 20. Negative Control Response | Not rated | Negative controls were not required for the study. | NR | NR | NR |
| **Confounding/ variable control** | 21. Confounding variables in test setup and procedures | Medium | Initial food/water intake and respiratory rate were not reported but this is not likely to have a significant impact on results. | 2 | 2 | 4 |
| | 22. Outcomes unrelated to exposure | High[A] | | 1 | 1 | 1 |
| **Data presentation and analysis** | 23. Statistical methods | High | The data was provided, but statistical analysis is not required | 1 | 1 | 1 |
| | 24. Reporting of data | High[A] | | 1 | 2 | 2 |
| | | | **Sum of scores:** | **25** | **25** | **33** |
| High | Medium | Low | **Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:** | **1.320** | **Overall Score (Rounded):** | **1.3** |
| ≥1 and <1.7 | ≥1.7 and <2.3 | ≥2.3 and ≤3 | **Overall Quality Level:** | | | **HIGH** |
| Footnote A: This metric met the criteria for high confidence as expected for this type of study. | | | | | | |

**Table 12. Eye Irritation Study, (BASF, 1975c)**

| Study Reference: | BASF. 1975. Eye Irritation Study. BASF Report XXV/454. Product Safety Basel, BASF Schweiz AG, Switzerland. [as reported in Translated PV29 Tox Summaries, Product Safety Basel, BASF Schweiz AG, Switzerland, January 31, 2018]. HERO ID: 4731519 | | | | | |
|---|---|---|---|---|---|---|
| **Note:** | Study guideline was not indicated in the study report | | | | | |
| **Domain** | **Metric** | **Qualitative Determination [*i.e.*, High, Medium, Low, Unacceptable, or Not rated]** | **Comments** | **Metric Score** | **Metric Weighting Factor** | **Weighted Score** |
| **Test Substance** | 1. Test substance identity | Medium | CASRN number was provided (81-33-4) but other expected details were not discussed in the study. For instance, the physical nature of the test substance was not described but it is inferred to be solid state based on the physical/chemical properties of PV29. | 2 | 2 | 4 |
| | 2. Test substance source | Low | No details were provided about the source and lot number of the test substance. | 3 | 1 | 3 |
| | 3.Test substance purity | Low | No details were provided about the test substance purity. | 3 | 1 | 3 |
| **Test setup** | 4. Negative controls | High | The eye treated with talcum powder served as the negative control | 1 | 2 | 2 |
| | 5. Positive controls | Not rated | Positive control animals are not required for this study. | NR | NR | NR |
| | 6. Randomized allocation | Not rated | Only two individual animals were tested, so randomization is typically not required. | NR | NR | NR |
| **Exposure characterization** | 7. Preparation and storage of test substance | Low | The study did not discuss details about the preparation and/or storage conditions of the test substance. | 3 | 1 | 3 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 8. Consistency of Exposure administration | High[A] | | 1 | 1 | 1 |
| | 9. Reporting of doses / concentrations | High[A] | | 1 | 2 | 2 |
| | 10. Exposure frequency and duration | High[A] | | 1 | 1 | 1 |
| | 11. Number of exposure groups and dose spacing | High | The test typically applies a single dose to one of the eyes of the experimental animal. | 1 | 1 | 1 |
| | 12. Exposure route and method | High[A] | | 1 | 1 | 1 |
| **Test organisms** | 13. Test animal characteristics | Low | Study provided minimal information on the test animal characteristics (*e.g.*, strain, health status, age). | 3 | 2 | 6 |
| | 14. Adequacy and consistency of animal husbandry conditions | Low | Study provided minimal information on the adequacy of animal husbandry conditions. | 3 | 1 | 3 |
| | 15. Number per group | Medium | Generally at least three animals are used for eye irritation tests. But in this case, study authors used only 2 animals. | 2 | 1 | 2 |
| **Outcome Assessment** | 16. Outcome assessment methodology | Medium | The method used to score irritation was not discussed. However, it is understood the scoring scale as it is standard for the eye irritation tests. Other details were not discussed (*e.g.*, criteria for study termination). | 2 | 2 | 4 |
| | 17. Consistency of outcome assessment | Medium | It is inferred that the control (n=1) and treated (n=1) were exposed using the | 2 | 1 | 2 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | same method based on details provided in the study. However, the study did not address the measures that the investigators put in place (*e.g.*, training of staff in scoring) to have consistency in the outcome assessment. | | | |
| | 18. Sampling adequacy | High | Only two animals were used and in each case one eye was used for test substance and one eye for control substance. The reviewers monitored the animals during and after treatment from 10 min onwards till day 8th. | 1 | 1 | 1 |
| | 19. Blinding of assessors | Not rated | It is not discussed in these studies. Note that the grading of ocular responses is subjective. Training in observing the ocular responses and translating them to a score promotes harmonization of subjective results. | NR | NR | NR |
| | 20. Negative Control Response | High[A] | | 1 | 1 | 1 |
| **Confounding/ variable control** | 21. Confounding variables in test setup and procedures | Low | It is not possible to determine if there were confounding variables with the limited information given in the report. | 3 | 2 | 6 |
| | 22. Outcomes unrelated to exposure | Low | It is not possible to determine if there were confounding variables with the limited information given in the report. | 3 | 1 | 3 |
| **Data presentation and analysis** | 23. Statistical methods | Not rated | Data not amenable for statistics | NR | NR | NR |
| | 24. Reporting of data | High | Ocular responses were reported for | 1 | 2 | 2 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | control and treated eyes in both female rabbits. | | | |
| | | | **Sum of scores:** | **38** | **27** | **51** |
| High | Medium | Low | **Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:** | **1.889** | **Overall Score (Rounded):** | **1.9** |
| ≥1 and <1.7 | ≥1.7 and <2.3 | ≥2.3 and ≤3 | **Overall Quality Level:** | | | **Medium** |
| Footnote A: This metric met the criteria for high confidence as expected for this type of study. | | | | | | |

**Table 13. Eye Irritation Study, (BASF, 1978a)**

| Study Reference: | BASF. 1978. Eye Irritation Study. BASF Report 77/360. Product Safety Basel, BASF Schweiz AG, Switzerland. [as reported in Translated PV29 Tox Summaries, Product Safety Basel, BASF Schweiz AG, Switzerland, January 31, 2018]. HERO ID: 4731520 | | | | | |
|---|---|---|---|---|---|---|
| **Note:** | Study guideline was not indicated in the study report | | | | | |
| **Domain** | **Metric** | **Qualitative Determination [*i.e.*, High, Medium, Low, Unacceptable, or Not rated]** | **Comments** | **Metric Score** | **Metric Weighting Factor** | **Weighted Score** |
| **Test Substance** | 1. Test substance identity | Medium | CASRN number was provided (81-33-4) but other expected details were not discussed in the study. For instance, the physical nature of the test substance was not described but it is inferred to be solid state based on the physical/chemical properties of PV29. | 2 | 2 | 4 |
| | 2. Test substance source | Low | No details were provided about the source and lot number of the test substance. | 3 | 1 | 3 |
| | 3.Test substance purity | Low | No details were provided about the test substance purity. | 3 | 1 | 3 |
| **Test setup** | 4. Negative controls | High | The eye treated with talcum powder served as the negative control | 1 | 2 | 2 |
| | 5. Positive controls | Not rated | Positive control animals are not required for the test type. | NR | NR | NR |
| | 6. Randomized allocation | Not rated | Only two individual animals were tested, so randomization is typically not required. | NR | NR | NR |
| **Exposure characterization** | 7. Preparation and storage of test substance | Low | The study did not discuss details about the preparation and/or storage conditions of the test substance. | 3 | 1 | 3 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 8. Consistency of Exposure administration | High[A] | | 1 | 1 | 1 |
| | 9. Reporting of doses / concentrations | High[A] | | 1 | 2 | 2 |
| | 10. Exposure frequency and duration | High[A] | | 1 | 1 | 1 |
| | 11. Number of exposure groups and dose spacing | High | The test typically applies a single dose to one of the eyes of the experimental animal. | 1 | 1 | 1 |
| | 12. Exposure route and method | High[A] | | 1 | 1 | 1 |
| **Test organisms** | 13. Test animal characteristics | Low | Study provided minimal information on the test animal characteristics (*e.g.*, strain, health status, age). | 3 | 2 | 6 |
| | 14. Adequacy and consistency of animal husbandry conditions | Low | Study provided minimal information on the adequacy of animal husbandry conditions. | 3 | 1 | 3 |
| | 15. Number per group | High | Three animals were tested, each animal received test substance in one eye and Talcum powder as control in the other eye. | 1 | 1 | 1 |
| **Outcome Assessment** | 16. Outcome assessment methodology | Medium | The method used to score irritation was not discussed. However, it is understood the scoring scale as it is standard for the eye irritation tests. Other details were not discussed (*e.g.*, criteria for study termination). | 2 | 2 | 4 |
| | 17. Consistency of outcome assessment | Medium | It is inferred that the control (n=1) and treated (n=1) were exposed using the | 2 | 1 | 2 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | same method based on details provided in the study. However, the study did not address the measures that the investigators put in place (*e.g.*, training of staff in scoring) to have consistency in the outcome assessment. | | | |
| | 18. Sampling adequacy | High | Three animals were used and in each case one eye was used for test substance and one eye for control substance. The reviewers monitored the animals during and after treatment at different timepoints. | 1 | 1 | 1 |
| | 19. Blinding of assessors | Not Rated | It is not discussed in these studies. Note that the grading of ocular responses is subjective. Training in observing the ocular responses and translating them to a score promotes harmonization of subjective results. | NR | NR | NR |
| | 20. Negative Control Response | High[A] | | 1 | 1 | 1 |
| **Confounding/ variable control** | 21. Confounding variables in test setup and procedures | Low | It is not possible to determine if there were confounding variables with the limited information given in the report. | 3 | 2 | 6 |
| | 22. Outcomes unrelated to exposure | Low | It is not possible to determine if there were confounding variables with the limited information given in the report. | 3 | 1 | 3 |
| **Data presentation and analysis** | 23. Statistical methods | Not rated | Data not amenable for statistics | NR | NR | NR |
| | 24. Reporting of data | High | Ocular responses were reported for | 1 | 2 | 2 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | control and treated eyes in male rabbits. | | | |
| | | | **Sum of scores:** | **37** | **27** | **50** |
| High | Medium | Low | **Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:** | **1.852** | **Overall Score (Rounded):** | **1.9** |
| ≥1 and <1.7 | ≥1.7 and <2.3 | ≥2.3 and ≤3 | **Overall Quality Level:** | | | **Medium** |
| Footnote A: This metric met the criteria for high confidence as expected for this type of study. | | | | | | |

**Table 14. Eye Irritation Study, (Rupprich and Weigand, 1984b)**

| Study Reference: | Rupprich, N, Weigand, W. 1984. Perylimid Testing the acute irritant effects/caustic effects on the rabbit eye. Hoechst Pharma Research Toxicology, Germany. Report No. 84.0229. For Farben Nord, Werk Höchst. HERO ID: 4731524 | | | | | |
|---|---|---|---|---|---|---|
| **Note:** | Test was conducted according to the OECD TG 405 Acute Eye Irritation / Corrosion (1981) | | | | | |
| **Domain** | **Metric** | **Qualitative Determination [*i.e.*, High, Medium, Low, Unacceptable, or Not rated]** | **Comments** | **Metric Score** | **Metric Weighting Factor** | **Weighted Score** |
| **Test Substance** | 1. Test substance identity | High | The test substance was identified definitively and the specific form was characterized. | 1 | 2 | 2 |
| | 2. Test substance source | Medium | Source was incompletely reported. | 2 | 1 | 2 |
| | 3.Test substance purity | Medium | Product contained 80% active ingredient (Perylimid); other components were reported as 10% KOH, 8% diverse organic contaminations, which were not identified, approx 1% inorganic salts, and approx 1% water. | 2 | 1 | 2 |
| **Test setup** | 4. Negative controls | High | The untreated eye served as the negative control. | 1 | 2 | 2 |
| | 5. Positive controls | Not Rated | Positive controls not required for the study. | NR | NR | NR |
| | 6. Randomized allocation | Not Rated | Only one group was included, so randomization is typically not required. | NR | NR | NR |
| **Exposure characterization** | 7. Preparation and storage of test substance | Low* | Details regarding storage conditions of the test substance in saline were not reported, neither was timeframe between formulation | 3 | 1 | 3 |

| Study Reference: | Rupprich, N, Weigand, W. 1984. Perylimid Testing the acute irritant effects/caustic effects on the rabbit eye. Hoechst Pharma Research Toxicology, Germany. Report No. 84.0229. For Farben Nord, Werk Höchst. HERO ID: 4731524 | | | | | |
|---|---|---|---|---|---|---|
| | | | preparation and use. Amount applied was given but the storage and solubility was not given. 100mg may not dissolve in 0.05ml of 0.9% NaCl solution. | | | |
| | 8. Consistency of Exposure administration | High[A] | | 1 | 1 | 1 |
| | 9. Reporting of doses / concentrations | High | 100mg was applied in 0.3ml of 0.9% NaCl solution | 1 | 2 | 2 |
| | 10. Exposure frequency and duration | High[A] | | 1 | 1 | 1 |
| | 11. Number of exposure groups and dose spacing | High[A] | | 1 | 1 | 1 |
| | 12. Exposure route and method | High[A] | | 1 | 1 | 1 |
| **Test organisms** | 13. Test animal characteristics | Medium | Details were not reported including age and sex. | 2 | 2 | 4 |
| | 14. Adequacy and consistency of animal husbandry conditions | High | Husbandry conditions were reported | 1 | 1 | 1 |
| | 15. Number per group | High[A] | | 1 | 1 | 1 |
| **Outcome Assessment** | 16. Outcome assessment methodology | High[A] | | 1 | 2 | 2 |
| | 17. Consistency of outcome assessment | High[A] | | 1 | 1 | 1 |
| | 18. Sampling adequacy | High[A] | | 1 | 1 | 1 |

| Study Reference: | Rupprich, N, Weigand, W. 1984. Perylimid Testing the acute irritant effects/caustic effects on the rabbit eye. Hoechst Pharma Research Toxicology, Germany. Report No. 84.0229. For Farben Nord, Werk Höchst. HERO ID: 4731524 | | | | | |
|---|---|---|---|---|---|---|
| | 19. Blinding of assessors | Not Rated | No subjective outcomes were assessed. | NR | NR | NR |
| | 20. Negative Control Response | High[A] | | 1 | 1 | 1 |
| **Confounding/ variable control** | 21. Confounding variables in test setup and procedures | High[A] | | 1 | 2 | 2 |
| | 22. Outcomes unrelated to exposure | High[A] | | 1 | 1 | 1 |
| **Data presentation and analysis** | 23. Statistical methods | High | The data was provided, but statistical analysis is not required | 1 | 1 | 1 |
| | 24. Reporting of data | High[A] | | 1 | 2 | 2 |
| | | | **Sum of scores:** | **26** | **28** | **34** |
| High | Medium | Low | **Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:** | **1.214** | **Overall Score (Rounded):** | **1.2** |
| ≥1 and <1.7 | ≥1.7 and <2.3 | ≥2.3 and ≤3 | **Overall Quality Level:** | | | **HIGH** |
| Footnote A: This metric met the criteria for high confidence as expected for this type of study. | | | | | | |

**Table 15. Local Lymph Node Assay, (Johnson, 1999)**

| Study Reference: | Johnson, I.R. 1999. Perylimid F: Local Lymph Node Assay. Central Toxicology Laboratory, UK. Project No. CTL/P/6194. For BASF Aktiengesellschaft, Germany. HERO ID: 4731537. | | | | | |
|---|---|---|---|---|---|---|
| **Note:** | Study report indicates that test was conducted according to OECD TG 406: Skin sensitization (1992) | | | | | |
| **Domain** | **Metric** | **Qualitative Determination [*i.e.*, High, Medium, Low, Unacceptable, or Not rated]** | **Comments** | **Metric Score** | **Metric Weighting Factor** | **Weighted Score** |
| **Test Substance** | 1. Test substance identity | High | The test substance was identified definitively and the specific form was characterized | 1 | 2 | 2 |
| | 2. Test substance source | High | Test item was received by the submitter and the batch number was provided. | 1 | 1 | 1 |
| | 3.Test substance purity | High | Given as 90% and the dose calculations were adjusted to purity | 1 | 1 | 1 |
| **Test setup** | 4. Negative and vehicle controls | High[A] | | 1 | 2 | 2 |
| | 5. Positive controls | High | Positive control study was conducted within 6 months of study and was appropriate. | 1 | 1 | 1 |
| | 6. Randomized allocation | Low | Allocation of animals into study groups was not reported. | 3 | 1 | 3 |
| **Exposure characterization** | 7. Preparation and storage of test substance | Medium | Details regarding storage conditions of the test | 2 | 1 | 2 |

| Study Reference: | Johnson, I.R. 1999. Perylimid F: Local Lymph Node Assay. Central Toxicology Laboratory, UK. Project No. CTL/P/6194. For BASF Aktiengesellschaft, Germany. HERO ID: 4731537. | | | | | |
|---|---|---|---|---|---|---|
| | | | substance in propylene glycol were not reported. | | | |
| | 8. Consistency of exposure administration | High[A] | | 1 | 1 | 1 |
| | 9. Reporting of doses / concentrations | High | The administered doses were reported without ambiguity. | 1 | 2 | 2 |
| | 10. Exposure frequency and duration | High[A] | | 1 | 1 | 1 |
| | 11. Number of exposure groups and dose spacing | High | It is unclear fi the highest concentration was high enough to induce a response. | 1 | 1 | 1 |
| | 12. Exposure route and method | High | The route and method of exposure were reported. | 1 | 1 | 1 |
| **Test organisms** | 13. Test animal characteristics | Medium | Details were not reported including age, health status, and starting body weight. | 2 | 2 | 4 |
| | 14. Adequacy and consistency of animal husbandry conditions | High[A] | All husbandry conditions were reported and the only difference was the exposure. | 1 | 1 | 1 |
| | 15. Number per group | High[A] | | 1 | 1 | 1 |
| **Outcome Assessment** | 16. Outcome assessment methodology | High | The outcome assessment methodology addressed the intended outcomes of interest and | 1 | 2 | 2 |

| Study Reference: | Johnson, I.R. 1999. Perylimid F: Local Lymph Node Assay. Central Toxicology Laboratory, UK. Project No. CTL/P/6194. For BASF Aktiengesellschaft, Germany. HERO ID: 4731537. | | | | | |
|---|---|---|---|---|---|---|
| | | | was sensitive for the outcome of interest. | | | |
| | 17. Consistency of outcome assessment | High | Details of the outcome of assessment protocols and reported outcomes were assessed consistently. | 1 | 1 | 1 |
| | 18. Sampling adequacy | High[A] | | 1 | 1 | 1 |
| | 19. Blinding of assessors | Not rated | It is not typically discussed in these studies. | NR | NR | NR |
| | 20. Negative control response | High | The biological responses of the negative control group were adequate. | 1 | 1 | 1 |
| **Confounding/ variable control** | 21. Confounding variables in test setup and procedures | High[A] | | 1 | 2 | 2 |
| | 22. Outcomes unrelated to exposure | High | Due to heavy precipitation of the test substance the bacterial lawn could only be evaluated to the penultimate highest dose. | 1 | 1 | 1 |
| **Data presentation and analysis** | 23. Statistical methods | High | The data was reported, but the statistically analysis was not required as the test substance did not cause significant change. | 1 | 1 | 1 |

| Study Reference: | Johnson, I.R. 1999. Perylimid F: Local Lymph Node Assay. Central Toxicology Laboratory, UK. Project No. CTL/P/6194. For BASF Aktiengesellschaft, Germany. HERO ID: 4731537. | | | | | |
|---|---|---|---|---|---|---|
| | 24. Reporting of data | High | Data was presented for all outcomes. | 1 | 2 | 2 |
| | | | **Sum of scores:** | **27** | **30** | **35** |
| High | Medium | Low | **Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:** | **1.167** | **Overall Score (Rounded):** | **1.2** |
| ≥1 and <1.7 | ≥1.7 and <2.3 | ≥2.3 and ≤3 | **Overall Quality Level:** | | | **HIGH** |
| Footnote A: This metric met the criteria for high confidence as expected for this type of study. | | | | | | |

**Table 16. Study of the Mutagenic Potential in Strains of Salmonella typhimurium (AMES Test) and Escherichia coli, (Jung and Weigand, 1983)**

| Study Reference: | Jung, R., Weigand, W. 1983. Perylimid Study of the Mutagenic Potential in Strains of *Salmonella typhimurium* (AMES Test) and *Escherichia coli*. Hoechst Aktiengesellschaft, Germany. Report No. 83.0695. For Hoechst, Fahrenforschung, Germany. HERO ID: 4731535. | | | | | |
|---|---|---|---|---|---|---|
| **Note:** | Study report did not indicate the authors followed a test guideline | | | | | |
| **Domain** | **Metric** | **Qualitative Determination [*i.e.*, High, Medium, Low, Unacceptable, or Not rated]** | **Comments** | **Metric Score** | **Metric Weighting Factor** | **Weighted Score** |
| **Test Substance** | 1. Test substance identity | High | The test substance was identified definitively and the specific form was characterized | 1 | 2 | 2 |
| | 2. Test substance source | Medium | The source was incompletely reported. | 2 | 1 | 2 |
| | 3.Test substance purity | High | See note at the bottom of the table. | 1 | 1 | 1 |
| **Test setup** | 4. Negative controls | High | Solvent control was used as negative control | 1 | 2 | 2 |
| | 5. Positive controls | High | The positive controls were included and the response was appropriate. | 1 | 2 | 2 |
| | 6. Assay procedure | High[A] | | 1 | 1 | 1 |
| | 7. Standards for test | Not rated | This metric is not applicable for this endpoint | NR | NR | NR |
| **Exposure characterization** | 8. Preparation and storage of test substance | Medium | The test substance was prepared on the day of the test, but storage information | 2 | 1 | 2 |

| Study Reference: | Jung, R., Weigand, W. 1983. Perylimid Study of the Mutagenic Potential in Strains of *Salmonella typhimurium* (AMES Test) and *Escherichia coli*. Hoechst Aktiengesellschaft, Germany. Report No. 83.0695. For Hoechst, Fahrenforschung, Germany. HERO ID: 4731535. | | | | | |
|---|---|---|---|---|---|---|
| | | | was not provided. | | | |
| | 9. Consistency of exposure administration | High[A] | | 1 | 1 | 1 |
| | 10. Reporting of concentrations | High | The tested doses were reported without ambiguity. | 1 | 2 | 2 |
| | 11. Exposure duration | High | 48 to 72hr with and without metabolic activation. | 1 | 2 | 2 |
| | 12. Number of exposure groups and dose spacing | High[A] | | 1 | 1 | 1 |
| | 13. Metabolic activation | High | Metabolic activation is reported and performed using Mammalian Microsomal Fraction S9 Mix | 1 | 1 | 1 |
| **Test Model** | 14. Test model | High | Bacterial and Salmonella typhimurium was chosen based on historical success in in vitro experiments. | 1 | 2 | 2 |
| | 15. Number per group | High | The number of exposed cells/ replicate was not reported. The number of replicates/ concentration was appropriate. | 1 | 1 | 1 |

| Study Reference: | Jung, R., Weigand, W. 1983. Perylimid Study of the Mutagenic Potential in Strains of *Salmonella typhimurium* (AMES Test) and *Escherichia coli*. Hoechst Aktiengesellschaft, Germany. Report No. 83.0695. For Hoechst, Fahrenforschung, Germany. HERO ID: 4731535. | | | | | |
|---|---|---|---|---|---|---|
| **Outcome Assessment** | 16. Outcome assessment methodology | High | The outcome assessment methodology addressed the intended outcome of interest and was sensitive | 1 | 2 | 2 |
| | 17. Consistency of outcome assessment | High | Details of the outcome of assessment protocols and reported outcomes were assessed consistently | 1 | 1 | 1 |
| | 18. Sampling adequacy | High[A] | | 1 | 2 | 2 |
| | 19. Blinding of assessors | Not rated | It is not typically discussed in these studies. | NR | NR | NR |
| **Confounding/ variable control** | 20. Confounding variables in test setup and procedures | High[A] | | 1 | 2 | 2 |
| | 21. Confounding variables in outcomes unrelated to exposure | High[A] | | 1 | 1 | 1 |
| **Data presentation and analysis** | 22. Data analysis | High | Statistical methods, calculation and methods were not required | 1 | 1 | 1 |
| | 23. Data interpretation | High | Evaluation criteria appeared to be limited to positive controls, defined as a significant increase in | 1 | 2 | 2 |

| Study Reference: | Jung, R., Weigand, W. 1983. Perylimid Study of the Mutagenic Potential in Strains of *Salmonella typhimurium* (AMES Test) and *Escherichia coli*. Hoechst Aktiengesellschaft, Germany. Report No. 83.0695. For Hoechst, Fahrenforschung, Germany. HERO ID: 4731535. | | | | | |
|---|---|---|---|---|---|---|
| | | | revertant colonies | | | |
| | 24. Cytotoxicity data | Not rated | This was not a cytotoxicity test rather a mutagenicity test. this Metric should not be applied | NR | NR | NR |
| | 25. Reporting of data | High[A] | | 1 | 2 | 2 |
| | | | **Sum of scores:** | **23** | **33** | **35** |
| High | Medium | Low | **Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:** | **1.061** | **Overall Score (Rounded):** | **1.1** |
| ≥1 and <1.7 | ≥1.7 and <2.3 | ≥2.3 and ≤3 | **Overall Quality Level:** | | | **HIGH** |
| Footnote A: This metric met the criteria for high confidence as expected for this type of study. | | | | | | |

**Table 17. Gene Mutation Assay in Chinese Hamster V79 Cells In Vitro, (Wollny, 2012)**

| Study Reference: | Wollny, H. 2012. Gene Mutation Assay in Chinese Hamster V79 Cells In Vitro (V79/HPRT) with Paliogen Violet 5011. Harlan Cytotest Cell Research GmbH, Germany. Report No. 1443105. For BASF SE, Germany. HERO ID: 4731536. | | | | | |
|---|---|---|---|---|---|---|
| **Note:** | Study report indicates it was conducted according to OECD TG 467/ OPPTS 870.5300 | | | | | |
| **Domain** | **Metric** | **Qualitative Determination [*i.e.*, High, Medium, Low, Unacceptable, or Not rated]** | **Comments** | **Metric Score** | **Metric Weighting Factor** | **Weighted Score** |
| **Test Substance** | 1. Test substance identity | High | The test substance was identified definitively, and the specific form was characterized | 1 | 2 | 2 |
| | 2. Test substance source | Medium | The source was incompletely reported. | 2 | 1 | 2 |
| | 3.Test substance purity | High | Given as 90% and the dose calculations were adjusted to purity | 1 | 1 | 1 |
| **Test setup** | 4. Negative controls | High | Solvent control was used as negative control | 1 | 2 | 2 |
| | 5. Positive controls | High | The positive controls were included and the response was appropriate (induction of positive effect). | 1 | 2 | 2 |
| | 6. Assay procedure | High[A] | | 1 | 1 | 1 |
| | 7. Standards for test | High | Mutant colonies per 106 cell identified in solvent control should be within the laboratory historical controls and positive control substance is expected to produce significant increase in | 1 | 1 | 1 |

| Study Reference: | Wollny, H. 2012. Gene Mutation Assay in Chinese Hamster V79 Cells In Vitro (V79/HPRT) with Paliogen Violet 5011. Harlan Cytotest Cell Research GmbH, Germany. Report No. 1443105. For BASF SE, Germany. HERO ID: 4731536. | | | | | |
|---|---|---|---|---|---|---|
| | | | mutant colony frequency. | | | |
| **Exposure characterization** | 8. Preparation and storage of test substance | Medium | The test substance was prepared on the day of the test, but storage information was not provided. | 2 | 1 | 2 |
| | 9. Consistency of exposure administration | High[A] | | 1 | 1 | 1 |
| | 10. Reporting of concentrations | High | The tested doses were reported without ambiguity. | 1 | 2 | 2 |
| | 11. Exposure duration | High | 4hr and 24hr with and without metabolic activation | 1 | 2 | 2 |
| | 12. Number of exposure groups and dose spacing | High[A] | | 1 | 1 | 1 |
| | 13. Metabolic activation | High | Metabolic activation is reported and performed using Mammalian Microsomal Fraction S9 Mix | 1 | 1 | 1 |
| **Test Model** | 14. Test model | High | V79 cell line was chosen based on historical success in in vitro experiments. | 1 | 2 | 2 |
| | 15. Number per group | High | The number of exposed cells/replicates was not reported. The number of replicates/ concentration was appropriate | 1 | 1 | 1 |
| **Outcome Assessment** | 16. Outcome assessment methodology | High | The outcome assessment methodology | 1 | 2 | 2 |

| Study Reference: | Wollny, H. 2012. Gene Mutation Assay in Chinese Hamster V79 Cells In Vitro (V79/HPRT) with Paliogen Violet 5011. Harlan Cytotest Cell Research GmbH, Germany. Report No. 1443105. For BASF SE, Germany. HERO ID: 4731536. | | | | | |
|---|---|---|---|---|---|---|
| | | | addressed the intended outcome of interest and was sensitive | | | |
| | 17. Consistency of outcome assessment | High | Details of the outcome of assessment protocols and reported outcomes were assessed consistently | 1 | 1 | 1 |
| | 18. Sampling adequacy | High[A] | | 1 | 2 | 2 |
| | 19. Blinding of assessors | Not rated | It is not typically discussed in these studies. | NR | NR | NR |
| **Confounding/ variable control** | 20. Confounding variables in test setup and procedures | High | There were no differences reported among study groups apart from precipitation of the test substance in the higher doses. | 1 | 2 | 2 |
| | 21. Confounding variables in outcomes unrelated to exposure | High[A] | | 1 | 1 | 1 |
| **Data presentation and analysis** | 22. Data analysis | High | Statistical methods, calculation and methods were presented | 1 | 1 | 1 |
| | 23. Data interpretation | High | Evaluation criteria appeared to be limited to positive controls, defined as a significant increase in revertant colonies | 1 | 2 | 2 |
| | 24. Cytotoxicity data | Not rated | This is not a cytotoxicity test rather a | NR | NR | NR |

| Study Reference: | Wollny, H. 2012. Gene Mutation Assay in Chinese Hamster V79 Cells In Vitro (V79/HPRT) with Paliogen Violet 5011. Harlan Cytotest Cell Research GmbH, Germany. Report No. 1443105. For BASF SE, Germany. HERO ID: 4731536. | | | | | |
|---|---|---|---|---|---|---|
| | | | mutagenicity test, \ so this metric is not applicable | | | |
| | 25. Reporting of data | High[A] | | 1 | 2 | 2 |
| | | | **Sum of scores:** | **24** | **34** | **36** |
| High | Medium | Low | **Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:** | **1.059** | **Overall Score (Rounded):** | **1.1** |
| ≥1 and <1.7 | ≥1.7 and <2.3 | ≥2.3 and ≤3 | **Overall Quality Level:** | | | **HIGH** |
| Footnote A: This metric met the criteria for high confidence as expected for this type of study. | | | | | | |

**Table 18. Effects of Subchronically Inhaled Carbon Black, (Elder et al., 2005)**

| Study Reference: | Elder et al., 2005. Effects of Subchronically Inhaled Carbon Black in Three Species. I. Retention Kinetics, Lung Inflammation, and Histopathology. HERO ID: 88194 | | | | | |
|---|---|---|---|---|---|---|
| **Note:** | This study analyzed the inhalation effects of Carbon Black, an analogue of C.I. Pigment Violet 29. | | | | | |
| **Domain** | **Metric** | **Qualitative Determination [*i.e.*, High, Medium, Low, Unacceptable, or Not rated]** | **Comments** | **Metric Score** | **Metric Weighting Factor** | **Weighted Score** |
| **Test Substance** | 1. Test substance identity | High | The test substance was identified definitively, and the specific form was characterized | 1 | 2 | 2 |
| | 2. Test substance source | High | The Test Substance source was reported | 1 | 1 | 1 |
| | 3.Test substance purity | High | Test substance purity was reported | 1 | 1 | 1 |
| **Test setup** | 4. Negative controls | High | Negative controls were reported | 1 | 2 | 2 |
| | 5. Positive controls | Not rated | Positive control animals are not required for this study. | NR | NR | NR |
| | 6. Randomized allocation | High | Test organisms were randomly allocated to exposure groups | 1 | 1 | 1 |
| **Exposure characterization** | 7. Preparation and storage of test substance | High | Test substance preparation was fully reported. | 1 | 1 | 1 |
| | 8. Consistency of Exposure administration | High | Details of exposure administration was fully reported. | 1 | 1 | 1 |
| | 9. Reporting of doses / concentrations | High [A] | | 1 | 2 | 2 |

| Study Reference: | Elder et al., 2005. Effects of Subchronically Inhaled Carbon Black in Three Species. I. Retention Kinetics, Lung Inflammation, and Histopathology. HERO ID: 88194 | | | | | |
|---|---|---|---|---|---|---|
| | 10. Exposure frequency and duration | High [A] | | 1 | 1 | 1 |
| | 11. Number of exposure groups and dose spacing | High [A] | | 1 | 1 | 1 |
| | 12. Exposure route and method | High [A] | | 1 | 1 | 1 |
| **Test organisms** | 13. Test animal characteristics | High [A] | | 1 | 2 | 2 |
| | 14. Adequacy and consistency of animal husbandry conditions | Not Assessed | | NA | NA | NA |
| | 15. Number per group | High [A] | | 1 | 1 | 1 |
| **Outcome Assessment** | 16. Outcome assessment methodology | High [A] | | 1 | 2 | 2 |
| | 17. Consistency of outcome assessment | High [A] | | 1 | 1 | 1 |
| | 18. Sampling adequacy | High [A] | | 1 | 1 | 1 |
| | 19. Blinding of assessors | High [A] | | 1 | 1 | 1 |
| | 20. Negative Control Response | High | No effects reported in controls | 1 | 1 | 1 |
| **Confounding/ variable control** | 21. Confounding variables in test setup and procedures | High | No confounding variables | 1 | 2 | 2 |
| | 22. Outcomes unrelated to exposure | Med | Not Reported | 2 | 1 | 2 |
| **Data presentation and analysis** | 23. Statistical methods | High [A] | | 1 | 1 | 1 |
| | 24. Reporting of data | High [A] | | 1 | 2 | 2 |
| | | | **Sum of scores:** | **23** | | **29** |
| High | Medium | Low | **Overall Score = Sum of Weighted Scores/Sum of** | **1.034** | **Overall Score (Rounded):** | **1** |

| Study Reference: | Elder et al., 2005. Effects of Subchronically Inhaled Carbon Black in Three Species. I. Retention Kinetics, Lung Inflammation, and Histopathology. HERO ID: 88194 | | | | | |
|---|---|---|---|---|---|---|
| | | | **Metric Weighting Factors:** | | | |
| ≥1 and <1.7 | ≥1.7 and <2.3 | ≥2.3 and ≤3 | | | **Overall Quality Level:** | **High** |
| Footnote A: This metric met the criteria for high confidence as expected for this type of study. | | | | | | |

**Table 19. Effects of Chronically Inhaled Carbon Black, (Nikula et al., 1995)**

| Study Reference: | Nikula et al., 1995. Comparative Pulmonary Toxicities and Carcinogenicities of Chronically Inhaled Diesel Exhaust and Carbon Black in F344 Rats. HERO ID: 76641 | | | | | |
|---|---|---|---|---|---|---|
| **Note:** | This study analyzed the inhalation effects of Carbon Black, an analogue of C.I. Pigment Violet 29. | | | | | |
| **Domain** | **Metric** | **Qualitative Determination [*i.e.*, High, Medium, Low, Unacceptable, or Not rated]** | **Comments** | **Metric Score** | **Metric Weighting Factor** | **Weighted Score** |
| **Test Substance** | 1. Test substance identity | High | Elftex-12 furnace black | 1 | 2 | 2 |
| | 2. Test substance source | High | Cabot (Boston, MA) | 1 | 1 | 1 |
| | 3.Test substance purity | Low | Not reported | 3 | 1 | 3 |
| **Test setup** | 4. Negative controls | High | Negative (sham) filtered air controls were reported | 1 | 2 | 2 |
| | 5. Positive controls | Not rated | Positive control animals are not required for this study. | NR | NR | NR |
| | 6. Randomized allocation | High | Test organisms were randomly allocated, stratified by body wt, to exposure groups | 1 | 1 | 1 |
| **Exposure characterization** | 7. Preparation and storage of test substance | Medium | Because generated as dry aerosol, preparation described as part of exposure administration, but storage not provided | 2 | 1 | 2 |
| | 8. Consistency of Exposure administration | High | Details of exposure administration were fully reported. | 1 | 1 | 1 |
| | 9. Reporting of doses / concentrations | High | Nominal & analytical | 1 | 2 | 2 |

| Study Reference: | Nikula et al., 1995. Comparative Pulmonary Toxicities and Carcinogenicities of Chronically Inhaled Diesel Exhaust and Carbon Black in F344 Rats. HERO ID: 76641 | | | | | |
|---|---|---|---|---|---|---|
| | | | concentrations reported | | | |
| | 10. Exposure frequency and duration | High | Duration & frequency reported (16/h/day, 5 d/week, for 24 months | 1 | 1 | 1 |
| | 11. Number of exposure groups and dose spacing | Medium | Number of exposure groups reported; dose spacing adequate in that conc. response observed, but no NOAEC established, so dose selection not optimal | 2 | 1 | 2 |
| | 12. Exposure route and method | High | Detail of inhalation exposure chamber & methods provided. | 1 | 1 | 1 |
| **Test organisms** | 13. Test animal characteristics | High | Reported Details about species, strain, sex, age, source provided | 1 | 2 | 2 |
| | 14. Adequacy and consistency of animal husbandry conditions | High | Reported | 1 | 1 | 1 |
| | 15. Number per group | High | Reported | 1 | 1 | 1 |
| **Outcome Assessment** | 16. Outcome assessment methodology | High | Reported | 1 | 2 | 2 |
| | 17. Consistency of outcome assessment | High | Consistent | 1 | 1 | 1 |
| | 18. Sampling adequacy | High | Adequate | 1 | 1 | 1 |

| Study Reference: | Nikula et al., 1995. Comparative Pulmonary Toxicities and Carcinogenicities of Chronically Inhaled Diesel Exhaust and Carbon Black in F344 Rats. HERO ID: 76641 | | | | | |
|---|---|---|---|---|---|---|
| | 19. Blinding of assessors | Low | Not Reported | 3 | 1 | 3 |
| | 20. Negative Control Response | High | Low incidence of effects reported in controls | 1 | 1 | 1 |
| **Confounding/ variable control** | 21. Confounding variables in test setup and procedures | High | Confounding variables for mutagenicity were assayed. | 1 | 2 | 2 |
| | 22. Outcomes unrelated to exposure | High | Spontaneous tumor formation in controls with age was reported | 1 | 1 | 1 |
| **Data presentation and analysis** | 23. Statistical methods | High | Reported | 1 | 1 | 1 |
| | 24. Reporting of data | High | Detailed Reporting | 1 | 2 | 2 |
| | | | **Sum of scores:** | **27** | | **33** |
| High | Medium | Low | **Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:** | **1.22** | **Overall Score (Rounded):** | **1** |
| ≥1 and <1.7 | ≥1.7 and <2.3 | ≥2.3 and ≤3 | | | **Overall Quality Level:** | **High** |
| Footnote A: This metric met the criteria for high confidence as expected for this type of study. | | | | | | |

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