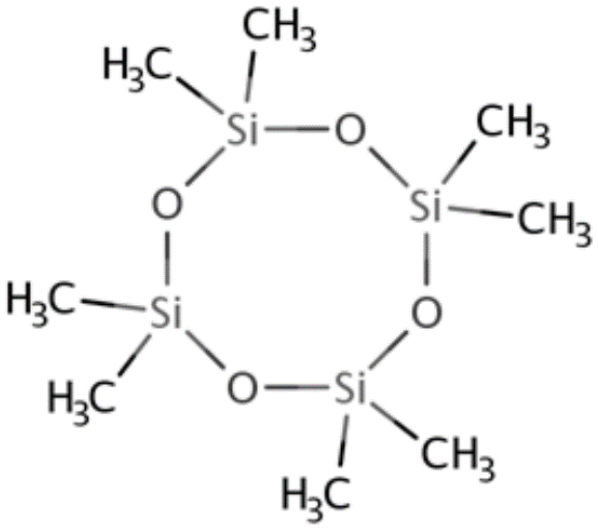
United States
Environmental Protection Agency

September 2025
Office of Chemical Safety and
Pollution Prevention

Data Quality Evaluation Information for Human Health Hazard Epidemiology for Octamethylcyclotetrasiloxane (D4)

Systematic Review Support Document for the Draft Risk Evaluation

CASRN: 556-67-2



September 2025

This supplemental file contains the data quality evaluation results for epidemiology data sources that met the PECO screening criteria and further filtering criteria for the *Draft Human Health Hazard Assessment for Octamethylcyclotetrasiloxane (D4)*. EPA conducted data quality evaluation based on author-reported descriptions and results; additional analyses (*e.g.*, statistical analyses performed during data integration into the risk evaluation) potentially conducted by EPA are not contained in this supplemental file. EPA used the TSCA systematic review process described in the *Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances* (also referred to as '2021 Draft Systematic Review Protocol'). Any updated steps in the systematic review process since the publication of the 2021 Draft Systematic Review Protocol are described in the *Draft Risk Evaluation for Octamethylcyclotetrasiloxane (D4) – Systematic Review Protocol*.

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Study Citation:	151 East Tenth Corp, (1974). Evaluation of potential hazards by dermal contact.
Health Outcome(s) Assessed:	Sensitization- Skin sensitization, Non-cancer; Irritation- Skin irritation, Non-cancer
Chemical:	Octamethylcyclotetrasiloxane (D4)- Parent compound
HERO ID:	5910551

Domain	Metric		Rating	Comments
Domain 1: Randomization				
	Metric 1A:	Was an adequate method used to randomize the administered dose or exposure level?	Medium	No randomization is required, as all subjects receive the dose and are assessed at the same point in time. There is no allocation to different groups.
Domain 2: Allocation Concealment and Blinding				
	Metric 2A:	Was allocation to study groups adequately concealed until recruitment was complete?	Medium	All subjects receive the same dose and are assessed at the same point in time. There is no allocation to different groups. Lack of adequate allocation concealment would not appreciably bias results.
	Metric 2B:	Were the research personnel and human subjects blinded to the study group during the study?	Medium	All subjects receive the same dose and are assessed at the same point in time. There is no allocation to different groups. Lack of adequate allocation concealment would not appreciably bias results.
Domain 3: Attrition				
	Metric 3A:	Were outcome data complete without attrition or exclusion from analysis?	High	Results are available for all subjects, and there is no reported attrition. Outcome and exposure data appear to be complete.
Domain 4: Exposure Measurement Bias				
	Metric 4A:	Can we be confident in the exposure characterization?	Low	The test subject, D4, was defined as ”volatile silicone 7207” and was reported to be used ”as supplied.” There is no discussion of purity testing or independent characterization, and the study does not specify how the chemical was retrieved (e.g. directly from manufacturer). Thus, there is insufficient information to determine the validity of the exposure assessment.
Domain 5: Outcome Assessment				
	Metric 5A:	Can we be confident in the outcome assessment?	Medium	This study used an induction patch test to assess sensitivity to D4. Subjects first received a repeated insult of D4 in a series of 15 occluded induction patches, followed by a challenge patch of D4 one week after the initial series of 15 patches. The induction patches were applied on Monday, Wednesday, and Friday with a contact period of 24 hours. Challenge patches were applied to the same spot as the induction patches were - positions were only changed if a reaction was reported. The challenge patch was observed for reaction after removal at 24 hours, and again 24 and 48 hours later. The scoring criteria for skin irritation reactions, including erythema and edema, were presented on a scale from 0-4, with definitions for each numerical score. While there is no description of the staff who assessed the patch test results, the methods utilized for this test are appropriate.

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Domain	Metric	Rating	Comments
	Metric 5B: Selective Reporting: Were all measured outcomes reported?	High	All outcomes discussed in the methods are reported in the results. Data are presented in a way that is suitable for full data extraction.

Additional Comments: This repeated insult patch test study of 200 human test subjects showed no clear concerns for bias. There were no concerns related to randomization, allocation, or concealment due to the patch-test design of the study. Exposure and outcome classification procedures are reasonably complete. The study reported that skin sensitization occurred in 2/200 eligible participants.

Overall Quality Determination Medium

Study Citation:	Corning,, Dow (1998). Non-regulated study: Immune effects of oral exposure of human volunteers to octamethylcyclotetrasiloxane (D4), with cover letter dated 12/04/1998.
Health Outcome(s) Assessed:	Renal/Kidney- Blood urea nitrogen, creatinine, uric acid, albumin, Non-cancer; Immune/Hematological- Total white blood cells, percentage of lymphocytes, helper T cells, suppressor T cells, B cells, NK cells, TNF-a, IL-6, serum amyloid A, IL-2, y-interferon, Non-cancer; Hepatic/Liver- AST, ALP, LDH, cholesterol, bilirubin, albumin, Non-cancer; Cardiovascular- LDH, cholesterol, Non-cancer; Clinical chemistry- Calcium, phosphorous, total protein, Non-cancer
Chemical:	Octamethylcyclotetrasiloxane (D4)- Parent compound
HERO ID:	5427169

Domain	Metric		Rating	Comments
Domain 1: Randomization				
	Metric 1A:	Was an adequate method used to randomize the administered dose or exposure level?	Medium	Participants in this double-blind, placebo-controlled, crossover study were stated to be randomized to the exposure or placebo group, but no description of the specific randomization process is provided.
Domain 2: Allocation Concealment and Blinding				
	Metric 2A:	Was allocation to study groups adequately concealed until recruitment was complete?	Medium	In this crossover study, patients served as their own controls and eventually received both the placebo and D4. Participants were exposed to either the placebo or D4 for the first two weeks of the study, after which exposures stopped for another two weeks. Then, during the last two week period, the groups switched so that the group that originally received the placebo received D4 during this period, and vice versa. While the initial allocation is not described specifically (i.e, whether they received the placebo or D4 first), there is no direct evidence that researchers knew which group subjects were allocated to, or whether subjects could infer which group they were allocated to.
	Metric 2B:	Were the research personnel and human subjects blinded to the study group during the study?	Medium	This study is reported to be ”double-blind”, indicating that neither the study researchers nor the subjects could infer which group they were allocated to. The study reports that blood and urine samples sent for laboratory analysis did not allow for researchers to ascertain the subject’s allocated group. While no other information is provided to ensure that blinding was successfully achieved, there is reasonable confidence that both subjects and researchers were unaware of subjects’ groups.
Domain 3: Attrition				
	Metric 3A:	Were outcome data complete without attrition or exclusion from analysis?	High	Exposure and outcome information is complete for all subjects, and no attrition is reported.
Domain 4: Exposure Measurement Bias				
	Metric 4A:	Can we be confident in the exposure characterization?	Medium	D4 was reported to be ”chemically pure” and was provided by the Dow Corning Corporation. A lot number is provided and the purity is stated to be 99.7%, although methods for determining purity are not described. Subjects received an oral syringe of D4 or placebo mixed with corn oil and a cherry flavoring in a dosage of 12 mg per day for 2 weeks. On weekends, subjects self-administered and returned empty syringes to the researchers. While it is possible that subjects did not actually consume the D4 on weekends, the researchers measured D4 in blood samples and found lower levels among those in the placebo group than those in the D4 group, implying the protocol was sufficiently followed to provide contrast between ”exposed” and ”unexposed” groups.
Domain 5: Outcome Assessment				

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Chemical:	Octamethylcyclotetrasiloxane (D4)- Parent compound
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Domain	Metric		Rating	Comments
	Metric 5A:	Can we be confident in the outcome assessment?	High	Relevant outcomes in this study were measured from blood samples for the analysis of clinical chemistry and hematological outcomes. Blood samples were collected daily, and were collected in heparinized vacutainers and delivered to the University of Rochester Medical Center's Clinical Chemistry laboratory within 90 minutes of blood draw. Given the medical laboratory setting, there can be a high degree of confidence in the validity of the clinical chemistry and hematology measures reported in this study.
	Metric 5B:	Selective Reporting: Were all measured outcomes reported?	High	All stated outcomes are reported in the results, and are tabulated in a manner that would be useful for data extraction and/or a potential meta-analysis.

Additional Comments: This placebo-controlled, randomized double-blind intentional dosing study used a crossover design to assess the effect of oral D4 on clinical chemistry and hematological parameters. The study overall has limited concerns for bias, as there is no evidence of deficiency in the randomization or allocation procedures, although there is no specific method provided for either process. There is reasonable confidence in the purity of D4, the determination of outcomes, and in concealment. The study reported no statistically significant associations between D4 exposure and clinical chemistry/hematology measures.

Overall Quality Determination High

Study Citation:	University of Rochester, (1997). Non-regulated study, clinical studies on the respiratory effects of octamethylcyclotetrasiloxane (D4) - mouth-piece and nasal exposures, with cover letter dated 10/2/1997.
Health Outcome(s) Assessed:	Lung/Respiratory- FVC, FEV1, Non-cancer; Lung/Respiratory- Cough, sputum production, shortness of breath, throat irritation, nasal congestion, wheezing, chest tightness, chest pain, Non-cancer; Ocular/Sensory- Eye irritation, Non-cancer; Neurological/Behavioral- Headache, Non-cancer; Musculoskeletal- Fatigue, Non-cancer; Gastrointestinal- Nausea, Non-cancer; Immune/Hematological- Complete blood cell count, CD4 count, CD8 count, CD3 count, CD56/16 count, CD19 count, erythrocyte sedimentation rate, C-reactive protein, interferon, TNF-a, IL-6, IL-2, Non-cancer; Hepatic/Liver- ALT, AST, Non-cancer; Renal/Kidney- Creatinine, blood urea nitrogen, Non-cancer
Chemical:	Octamethylcyclotetrasiloxane (D4)- Parent compound
HERO ID:	5887568

Domain	Metric		Rating	Comments
Domain 1: Randomization				
	Metric 1A:	Was an adequate method used to randomize the administered dose or exposure level?	Medium	Subjects were stated to be ”randomized” to either D4 or air exposure, but no specific method is described for randomization. Eventually, all participants received the exposure or placebo given the crossover design of the study. There is no evidence that subjects were allocated to receive D4 or air as their first or second exposure using non-random methods.
Domain 2: Allocation Concealment and Blinding				
	Metric 2A:	Was allocation to study groups adequately concealed until recruitment was complete?	Medium	This study used a crossover design, where all subjects received the exposure but at different times. There is no evidence to suggest that participants or research personnel were aware of whether subjects were exposed to D4 or air at a given time, and the study is reported to be ”double-blind.”
	Metric 2B:	Were the research personnel and human subjects blinded to the study group during the study?	Medium	The study is reported to be conducted under ”double-blind” conditions, although extensive details are not provided. There is no evidence that it was possible for research personnel or subjects to know whether they received D4 or air at a given time.
Domain 3: Attrition				
	Metric 3A:	Were outcome data complete without attrition or exclusion from analysis?	Medium	Exposure and outcome information is complete for all subjects, and no attrition is reported.
Domain 4: Exposure Measurement Bias				
	Metric 4A:	Can we be confident in the exposure characterization?	Medium	The study does not explicitly state where D4 was obtained, but the study was conducted in collaboration with the Dow Corning corporation, which produces D4, so there is reasonable confidence in the purity of D4 provided.Subjects were exposed to D4 via the inhalation route for 1 hour, delivered using a mouthpiece, at a dosage of 10 ppm. Subjects were exposed while exercising on a bicycle ergometer at a workload that was predetermined to triple the subjects resting minute ventilation in a prior screening session. Rest periods were utilized, with two exercise periods of 10 minutes each, and breaks of 10, 20, and 10 minutes. An alternate study was conducted to assess nasal exposure specifically, but the results from that study were only used to assess ADME information.
Domain 5: Outcome Assessment				

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Chemical:	Octamethylcyclotetrasiloxane (D4)- Parent compound
HERO ID:	5887568

Domain	Metric		Rating	Comments
	Metric 5A:	Can we be confident in the outcome assessment?	High	Hematology, immune, renal, and hepatic outcomes were measured from blood samples taken from subjects by a senior instructor physician during the exposure period. Samples were reported to be placed on ice and delivered to labs for analysis 1-6 hours after exposure. Detailed analytic methods are provided which do not indicate a high risk for outcome misclassification.The majority of the respiratory outcomes (cough, sputum production, shortness of breath, throat irritation, nasal congestion, wheezing, chest tightness, chest pain) as well as fatigue, headache, nausea, and eye irritation were measured via a self-administered questionnaire. A rating scale from 1-5 is provided that defines each point on the scale. A blank questionnaire is provided in the appendix, detailing the exact information patients had when completing the questionnaire.Other respiratory outcomes (FEV1, FVC) were measured before, immediately after exposure, and 24 hours post-exposure using a pneumotachograph, with extensive details provided on the set-up of the device.Overall, there is minimal concern for outcome misclassification across the outcomes reported in this study.
	Metric 5B:	Selective Reporting: Were all measured outcomes reported?	High	All outcomes mentioned in the methods are reported in the results. Results are fully tabulated in a manner that would allow for detailed data extraction.

Additional Comments: In this double-blind, placebo-controlled, crossover study, subjects were exposed to D4 via the inhalation route during exercise for 1 hour, and a wide variety of outcomes were measured, including pulmonary function, hematological/immunological parameters, and standard symptoms such as cough, headache, and fatigue. There are generally minimal concerns for bias in the study, with a sufficiently described approach to randomization, concealment, and blinding as well as a thorough description of the exposure paradigm and outcome assessment methods. The only significant effect reported in the paper was a lower level of AST when participants were exposed to air rather than D4.

Overall Quality Determination Medium