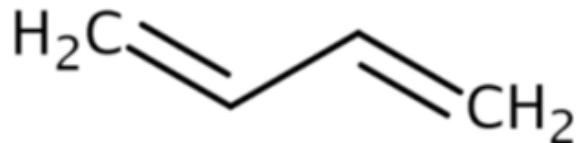

**Data Quality Evaluation Information for
Human Health Hazard Animal Toxicology for
1,3-Butadiene**

Systematic Review Support Document for the Risk Evaluation

CASRN: 106-99-0



December 2025

This supplemental file contains information regarding the data quality evaluation conducted for references that (1) met PECO screening criteria and (2) passed further filtering. For a detailed description on these criteria, see the [*Risk Evaluation for 1,3-Butadiene – Systematic Review Protocol*](#). 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) conducted by EPA are not contained in this supplemental file. For the data quality evaluation, 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 [*Risk Evaluation for 1,3-Butadiene - Systematic Review Protocol*](#).

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HERO ID	Reference	Page
1,3-Butadiene		
Acute (less than or equal to 24 hr)		
5663561	Anderson, D., Edwards, A. J., Brinkworth, M. H., Hughes, J. A. (1996). Male-mediated F1 effects in mice exposed to 1,3-butadiene. <i>Toxicology</i> 113(1-3):120-127.	5
4934798	Brinkworth, M. H., Anderson, D., Hughes, J. A., Jackson, L. I., Yu, T. W., Nieschlag, E. (1998). Genetic effects of 1,3-butadiene on the mouse testis. <i>Mutation Research</i> 397(1):67-75.	15
62368	Shugaev, B. B. (1969). Concentrations of hydrocarbons in tissues as a measure of toxicity. <i>Archives of Environmental and Occupational Health</i> 18(6):878-882.	18
Short-term (>1-30 days)		
62354	Hackett, P. L., Brown, M. G., Clark, M. L., Evanoff, J. J., Rowe, S. E., McClanahan, B. J., Buschbom, R. L., Decker, J. R., Rommereim, R. L., Westerberg, R. B. (1988). Sperm-head morphology study in B6C3F1 mice following inhalation exposure to 1,3-butadiene.	22
5663591	I-D, Adler, Filser, J., Gonda, H., Schriever-Schwemmer, G. (1998). Dose response study for 1,3-butadiene-induced dominant lethal mutations and heritable translocations in germs cells of male mice. <i>Mutation Research</i> 397(1):85-92.	26
1329207	Lee, J. H., Kang, H. S., Han, D. H. (2005). Ratios of N-(2,3,4-trihydroxybutyl) valine and N-(2-hydroxy-3-butenyl) valine formed hemoglobin adducts in female mice inhalation exposure with 1,3-butadiene. <i>Toxicology and Industrial Health</i> 21(1):15-20.	34
11273463	LRRI, (2005). [Redacted] 1,3-Butadiene: Whole-body inhalation exposure of rats and mice.	36
62372	National Institutes of Health,, Services,, D.o. (1984). Toxicology and carcinogenesis studies of 1,3-butadiene (CAS no. 106-99-0) in B6C3F1 mice (inhalation studies). <i>288:1-111.</i>	40
5553772	Pacchierotti, F., Tiveron, C., Ranaldi, R., Bassani, B., Cordelli, E., Leter, G., Spano, M. (1998). Reproductive toxicity of 1,3-butadiene in the mouse: Cytogenetic analysis of chromosome aberrations in first-cleavage embryos and flow cytometric evaluation of spermatogonial cell killing. <i>Mutation Research</i> 397(1):55-66.	43
Subchronic (>30-91 days)		
5663561	Anderson, D., Edwards, A. J., Brinkworth, M. H., Hughes, J. A. (1996). Male-mediated F1 effects in mice exposed to 1,3-butadiene. <i>Toxicology</i> 113(1-3):120-127.	49
5660612	Bevan, C., Stadler, J. C., Elliott, G. S., Frame, S. R., Baldwin, J. K., Leung, H. W., Moran, E., Panepinto, A. S. (1996). Subchronic toxicity of 4-vinylcyclohexene in rats and mice by inhalation exposure. <i>Fundamental and Applied Toxicology</i> 32(1):1-10.	58
4934798	Brinkworth, M. H., Anderson, D., Hughes, J. A., Jackson, L. I., Yu, T. W., Nieschlag, E. (1998). Genetic effects of 1,3-butadiene on the mouse testis. <i>Mutation Research</i> 397(1):67-75.	63
94760	Crouch, C. N., Pullinger, D. H., Gaunt, I. F. (1979). Inhalation toxicity studies with 1,3-butadiene - 2 3 month toxicity study in rats. <i>Journal of Occupational and Environmental Hygiene</i> 40(9):796-802.	69

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11273565	IBT Labs, (1977). Report to Tracor Jitco, Inc: Subchronic inhalation study with 1,3-butadiene (C50602) in B6C3F1 mice.	80
1419645	NTP, (1993). NTP Toxicology and Carcinogenesis Studies of 1,3-Butadiene (CAS No. 106-99-0) in B6C3F1 Mice (Inhalation Studies). National Toxicology Program Technical Report Series 434:1-389.	84
62366	Thurmond, L. M., Lauer, L. D., House, R. V., Stillman, W. S., Irons, R. D., Steinhagen, W. H., Dean, J. H. (1986). Effects of short-term inhalation exposure to 1,3-butadiene on murine immune functions. <i>Toxicology and Applied Pharmacology</i> 86(2):170-179.	89
Chronic (>91 days)		
62372	National Institutes of Health,, Services,, D.o. (1984). Toxicology and carcinogenesis studies of 1,3-butadiene (CAS no. 106-99-0) in B6C3F1 mice (inhalation studies). 288:1-111.	95
1419645	NTP, (1993). NTP Toxicology and Carcinogenesis Studies of 1,3-Butadiene (CAS No. 106-99-0) in B6C3F1 Mice (Inhalation Studies). National Toxicology Program Technical Report Series 434:1-389.	104
5554646	PNL,, Battelle (1982). Initial submission: Tracor Jitco inhalation carcinogenesis bioassay: Chronic study report in 1,3-butadiene in mice (final report) with attachments and cover letter dated 112191.	114
62366	Thurmond, L. M., Lauer, L. D., House, R. V., Stillman, W. S., Irons, R. D., Steinhagen, W. H., Dean, J. H. (1986). Effects of short-term inhalation exposure to 1,3-butadiene on murine immune functions. <i>Toxicology and Applied Pharmacology</i> 86(2):170-179.	120
Reproductive/Developmental		
1327602	Anderson, D., Hughes, J. A., Edwards, A. J., Brinkworth, M. H. (1998). A comparison of male-mediated effects in rats and mice exposed to 1,3-butadiene. <i>Mutation Research</i> 397(1):77-84.	126
5665017	BIBRA, (1996). Initial submission: the detection of dominant lethal mutations and * in the offspring of male mice treated subchronically with butadiene by inhalation, w/cover letter dated 1/10/97.	133
62371	Hazleton Labs, (1981). 1,3-Butadiene: Inhalation teratogenicity study in the rat (Final report).	145
62351	PNL,, Battelle (1987). Inhalation developmental toxicology studies: Teratology study of 1,3-butadiene in mice.	149
94731	PNL,, Battelle (1987). Inhalation developmental toxicology studies of 1,3-butadiene in the rat.	155
10367501	WIL Research, (2003). An inhalation reproduction/developmental toxicity screening study of 1,3-butadiene in rats.	161

Study Citation:	Anderson, D., Edwards, A. J., Brinkworth, M. H., Hughes, J. A. (1996). Male-mediated F1 effects in mice exposed to 1,3-butadiene. <i>Toxicology</i> 113(1-3):120-127.		
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Fetal skeletal abnormalities, % mated, % females pregnant, number of implantations, early and late deaths, late deaths including dead fetuses, number of abnormal fetuses.-Other (please specify below) (Genotoxicity)-Dominant lethality		
Duration and Exposure Route:	Inhalation-Gas-Duration: Acute (less than or equal to 24 hr)-F0- premating (6 hours)		
Species:	Mouse-CD-1 - [mouse]-Male		
Chemical:	1,3-Butadiene- Parent compound		
HERO ID:	5663561		
Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	Low	All critical and some important information was reported. The test material was identified as 1,3-butadiene in the title and abstract. A source was specified. CD-1 mice (sex and source reported) were acutely exposed, whole body, to 0, 1250, or 6,250 ppm for 6 hours. The number of animals per group was reported. Missing information included the test substance purity, animal age, starting body weights, parity of unexposed females, and all animal husbandry details. A citation was provided for standard practices (an IARC book publication). Endpoint evaluation methods and qualitative or quantitative results for at least one endpoint were reported. The missing information is expected to reduce the ability to evaluate the study.
Domain 2: Selection and Performance			
	Metric 2: Allocation	Low	The study did not report how animals were allocated into study groups, or if animals were normalized to body weight.
	Metric 3: Observational Bias / Blinding Changes	Medium	No blinding was mentioned in the study; however, no endpoints were subjective or blinding is not required according to current guidelines.
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	Low	Negative controls were exposed to ambient air only. Limited to no quantitative data were provided, so it is unclear whether the negative control responses were appropriate. The study monitored dimer concentrations in the exposure atmosphere and reported a range from 3 to 133 ppm (results per group were not specified). It is unclear what impact the presence of the dimer may have had on the study results. Although positive controls are generally not required for reproductive/developmental studies, this was a dominant lethality study, and positive controls are generally required (OECD TG 478). The authors did not indicate previous experience with this type of assay. Other details to determine confounding (e.g., animal body weights, and husbandry conditions) were not reported. Additionally, reflex bradypnea was not assessed; however, the chemical is a respiratory irritant in humans but not in animals.
Domain 4: Selective Reporting and Attrition			

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Study Citation: Anderson, D., Edwards, A. J., Brinkworth, M. H., Hughes, J. A. (1996). Male-mediated F1 effects in mice exposed to 1,3-butadiene. *Toxicology* 113(1-3):120-127.

Health Outcome(s) and Reported Health Effect(s): Reproductive/Developmental-Fetal skeletal abnormalities, % mated, % females pregnant, number of implantations, early and late deaths, late deaths including dead fetuses, number of abnormal fetuses.-Other (please specify below) (Genotoxicity)-Dominant lethality

Duration and Exposure Route: Inhalation-Gas-Duration: Acute (less than or equal to 24 hr)-F0- premating (6 hours)

Species: Mouse-CD-1 - [mouse]-Male

Chemical: 1,3-Butadiene- Parent compound

HERO ID: 5663561

Domain	Metric	Rating	Comments
	Metric 5: Selective Reporting and Attrition	Uninformative	Mortality was not assessed or reported. It is unknown whether any exposed males died due to attrition, although it was indicated that the "majority of animals were in good health." Additionally, no quantitative data for the acute exposure experiment were reported, and for most outcomes, no sample sizes were specified. Due to the extensive omission of results, no comparisons across treatment groups can be conducted.

Domain 5: Exposure Methods Sensitivity

Metric 6: Chemical administration and characterization	Low	Limited details on the test substance were provided. The source (ICI plc) no longer exists, and the test substance purity was not provided. The performing laboratory did not independently verify the test substance. The test atmospheres were monitored for the presence of the dimer, but no data reporting analytical measurements of the test substance were provided. It is unclear whether the reported concentrations were target or nominal. The chambers were described as being closed and animals were exposed whole body. It was not explicitly stated whether the chambers were static or dynamic. The number of animals per cage was not specified. Storage of the test substance was reported and was appropriate. The metric is uninformative to do the lack of details of the inhalation chamber.
Metric 7: Exposure timing, frequency, and duration	Uninformative	The study deviates significantly from OECD TG 478 for testing dominant lethality. Generally, to determine whether a chemical induces dominant lethality, animals should be exposed over an entire round of spermatogenesis (e.g., 7 weeks for mice), and then mated once. Single or acute exposures are generally done when the goal is to identify sensitive germ cell populations, and then animals are mated weekly (typically 8 matings after a single exposure). It is unclear that an acute exposure is appropriate for teratogenicity studies unless it is known what germ cell population is sensitive (e.g., if late stage or mature spermatozoa are not sensitive, then a single exposure followed by a single mating may not be appropriate for evaluating teratogenesis).

Domain 6: Outcome Measures and Results Display

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Study Citation:	Anderson, D., Edwards, A. J., Brinkworth, M. H., Hughes, J. A. (1996). Male-mediated F1 effects in mice exposed to 1,3-butadiene. <i>Toxicology</i> 113(1-3):120-127.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Fetal skeletal abnormalities, % mated, % females pregnant, number of implantations, early and late deaths, late deaths including dead fetuses, number of abnormal fetuses.-Other (please specify below) (Genotoxicity)-Dominant lethality
Duration and Exposure Route:	Inhalation-Gas-Duration: Acute (less than or equal to 24 hr)-F0- premating (6 hours)
Species:	Mouse-CD-1 - [mouse]-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	5663561

Domain	Metric	Rating	Comments
	Metric 8: Endpoint sensitivity and specificity	Low	This study conducted a modified dominant lethality assay. The authors describe the study design as one that "straddles the fields of genetic, reproductive, and developmental toxicity". Females were killed on GD17, rather than between GDs 12-15, allowing assessment of an additional classification of post-implantation deaths (i.e., dead fetuses: those that died immediately prior to examination). The outcome methods were generally consistent with those assessed in a standard dominant lethality study (OECD 428); however, methods were described with limited or confusing details. For example, skeletal malformations were assessed on (grossly) malformed fetuses and "randomly selected normal litter mates and controls;" the number of animals randomly selected is not clearly reported. The concentrations and concentration spacing were not explicitly justified. Only two groups were included, but current guidelines recommend 3. The animal species/strain and number of animals per group were adequate. The age and parity of females were not reported.
	Metric 9: Results presentation	Low	Results (primarily negative) were only described qualitatively in the text. Means and measures of variance were provided for the one endpoint in which an effect was observed. Statistical methods were not described in the methods section but were reported in tables reporting data from the subchronic duration experiments. It is assumed the same methods were applied to the data from the acute study. It was not specifically clear whether the statistical tests used the male as the experimental unit.

Overall Quality Determination

Uninformative

Study Citation:	Anderson, D., Edwards, A. J., Brinkworth, M. H., Hughes, J. A. (1996). Male-mediated F1 effects in mice exposed to 1,3-butadiene. <i>Toxicology</i> 113(1-3):120-127.		
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Body weights		
Duration and Exposure Route:	Inhalation-Gas-Duration: Acute (less than or equal to 24 hr)-F0- premating (6 hours)		
Species:	Mouse-CD-1 - [mouse]-Male		
Chemical:	1,3-Butadiene- Parent compound		
HERO ID:	5663561		
Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	Low	All critical and some important information was reported. The test material was identified as 1,3-butadiene in the title and abstract. A source was specified. CD-1 mice (sex and source reported) were acutely exposed, whole body, to 0, 1250, or 6,250 ppm for 6 hours. The number of animals per group was reported. Missing information included the test substance purity, animal age, starting body weights, parity of unexposed females, and all animal husbandry details. A citation was provided for standard practices (an IARC book publication). Endpoint evaluation methods and qualitative or quantitative results for at least one endpoint were reported. The missing information is expected to reduce the ability to evaluate the study.
Domain 2: Selection and Performance			
	Metric 2: Allocation	Low	The study did not report how animals were allocated into study groups, or if animals were normalized to body weight.
	Metric 3: Observational Bias / Blinding Changes	Medium	No blinding was mentioned in the study; however, no endpoints were subjective or blinding is not required according to current guidelines.
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	Low	Negative controls were exposed to ambient air only. No quantitative data were provided, so it is unclear whether the negative control responses were appropriate. The study monitored dimer concentrations in the exposure atmosphere and reported a range from 3 to 133 ppm (results per group were not specified). It is unclear what impact the presence of the dimer may have had on the study results. Although positive controls are generally not required for reproductive/developmental studies, this was a dominant lethality study, and positive controls are generally required (OECD TG 478). The authors did not indicate previous experience with this type of assay. Other details to determine confounding (e.g., animal body weights, and husbandry conditions) were not reported. Additionally, reflex bradypnea was not assessed; however, the chemical is a respiratory irritant in humans but not in animals.
Domain 4: Selective Reporting and Attrition			
	Metric 5: Selective Reporting and Attrition	Uninformative	Mortality was not assessed or reported. It is unknown whether any exposed males died due to attrition, although it was indicated that the "majority of animals were in good health." Additionally, no quantitative data for the acute exposure experiment were reported, and for most outcomes, no sample sizes were specified. Due to the extensive omission of results, no comparisons across treatment groups can be conducted.

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Study Citation:	Anderson, D., Edwards, A. J., Brinkworth, M. H., Hughes, J. A. (1996). Male-mediated F1 effects in mice exposed to 1,3-butadiene. <i>Toxicology</i> 113(1-3):120-127.		
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Body weights		
Duration and Exposure Route:	Inhalation-Gas-Duration: Acute (less than or equal to 24 hr)-F0- premating (6 hours)		
Species:	Mouse-CD-1 - [mouse]-Male		
Chemical:	1,3-Butadiene- Parent compound		
HERO ID:	5663561		
Domain	Metric	Rating	Comments
Domain 5: Exposure Methods Sensitivity			
Metric 6:	Chemical administration and characterization	Low	Limited details on the test substance were provided. The source (ICI plc) no longer exists, and the test substance purity was not provided. The performing laboratory did not independently verify the test substance. The test atmospheres were monitored for the presence of the dimer, but no data reporting analytical measurements of the test substance were provided. It is unclear whether the reported concentrations were target or nominal. The chambers were described as being closed and animals were exposed whole body. It was not explicitly stated whether the chambers were static or dynamic. The number of animals per cage was not specified. Storage of the test substance was reported and was appropriate.
Metric 7:	Exposure timing, frequency, and duration	Medium	The study deviates significantly from OECD TG 478 for testing dominant lethality. Generally, to determine whether a chemical induces dominant lethality, animals should be exposed over an entire round of spermatogenesis (e.g., 7 weeks for mice), and then mated once. Single or acute exposures are generally done when the goal is to identify sensitive germ cell populations, and then animals are mated weekly (typically 8 matings after a single exposure). It is unclear that an acute exposure is appropriate for teratogenicity studies unless it is known what germ cell population is sensitive (e.g., if late-stage or mature spermatozoa are not sensitive, then a single exposure followed by a single mating may not be appropriate for evaluating teratogenesis. For THIS outcome (body weight), exposure, timing and frequency were sufficient.
Domain 6: Outcome Measures and Results Display			
Metric 8:	Endpoint sensitivity and specificity	Low	This study conducted a modified dominant lethality assay. The authors describe the study design as one that "straddles the fields of genetic, reproductive, and developmental toxicity". Females were killed on GD17, rather than between GDs 12-15, allowing assessment of an additional classification of post-implantation deaths (i.e., dead fetuses: those that died immediately prior to examination). No mention of body weight measurements was mentioned in the methods; however, the results indicated that "no treatment-related effects were seen on the body weights of surviving animals (data not shown)." It is unclear which group of animals these results are referring to (exposed males, pregnant females?) or when, and at what frequency body weights were measured. The concentrations and concentration spacing were not explicitly justified. Only two groups were included, but current guidelines recommend 3. The animal species/strain and number of animals per group were adequate. The age and parity of females were not reported.

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Study Citation: Anderson, D., Edwards, A. J., Brinkworth, M. H., Hughes, J. A. (1996). Male-mediated F1 effects in mice exposed to 1,3-butadiene. *Toxicology* 113(1-3):120-127.

Health Outcome(s) and Reported Health Effect(s): Nutritional/Metabolic-Body weights

Duration and Exposure Route: Inhalation-Gas-Duration: Acute (less than or equal to 24 hr)-F0- premating (6 hours)

Species: Mouse-CD-1 - [mouse]-Male

Chemical: 1,3-Butadiene- Parent compound

HERO ID: 5663561

Domain	Metric	Rating	Comments
	Metric 9: Results presentation	Uninformative	A qualitative statement of "no treatment-related effects were seen on the body weights of surviving animals (data not shown)" was provided. It is unclear which group of animals these results are referring to (exposed males, pregnant females?). In the absence of methodological information on the outcome assessment in combination with poor data reporting, the results, as described, cannot be interpreted.

Overall Quality Determination

Uninformative

Study Citation:	Anderson, D., Edwards, A. J., Brinkworth, M. H., Hughes, J. A. (1996). Male-mediated F1 effects in mice exposed to 1,3-butadiene. <i>Toxicology</i> 113(1-3):120-127.		
Health Outcome(s) and Reported Health Effect(s):	Cancer/Carcinogenesis-Tumor incidence in F1 offspring		
Duration and Exposure Route:	Inhalation-Gas-Duration: Acute (less than or equal to 24 hr)-F0- premating (6 hours)		
Species:	Mouse-CD-1 - [mouse]-Male		
Chemical:	1,3-Butadiene- Parent compound		
HERO ID:	5663561		
Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	Low	All critical and some important information was reported. The test material was identified as 1,3-butadiene in the title and abstract. A source was specified. CD-1 mice (sex and source reported) were acutely exposed, whole body, to 0, 1250, or 6,250 ppm for 6 hours. The number of animals per group was reported. Missing information included the test substance purity, animal age, starting body weights, parity of unexposed females, and all animal husbandry details. A citation was provided for standard practices (an IARC book publication). Endpoint evaluation methods and qualitative or quantitative results for at least one endpoint were reported. The missing information is expected to reduce the ability to evaluate the study.
Domain 2: Selection and Performance			
	Metric 2: Allocation	Low	The study did not report how animals were allocated into study groups, or if animals were normalized to body weight.
	Metric 3: Observational Bias / Blinding Changes	Medium	No blinding was mentioned in the study; however, no endpoints were subjective or blinding is not required according to current guidelines.
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	Low	Negative controls were exposed to ambient air only. Limited to no quantitative data were provided, so it is unclear whether the negative control responses were appropriate. The study monitored dimer concentrations in the exposure atmosphere and reported a range from 3 to 133 ppm (results per group were not specified). It is unclear what impact the presence of the dimer may have had on the study results. Although positive controls are generally not required for reproductive/developmental studies, this was a dominant lethality study, and positive controls are generally required (OECD TG 478). The authors did not indicate previous experience with this type of assay. Other details to determine confounding (e.g., animal body weights, and husbandry conditions) were not reported. Additionally, reflex bradypnea was not assessed; however, the chemical is a respiratory irritant in humans but not in animals.
Domain 4: Selective Reporting and Attrition			
	Metric 5: Selective Reporting and Attrition	Uninformative	Mortality was not assessed or reported. It is unknown whether any exposed males died due to attrition, although it was indicated that the "majority of animals were in good health." Additionally, no quantitative data for the acute exposure experiment were reported, and for most outcomes, no sample sizes were specified. Due to the extensive omission of results, no comparisons across treatment groups can be conducted.

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Study Citation:	Anderson, D., Edwards, A. J., Brinkworth, M. H., Hughes, J. A. (1996). Male-mediated F1 effects in mice exposed to 1,3-butadiene. <i>Toxicology</i> 113(1-3):120-127.		
Health Outcome(s) and Reported Health Effect(s):	Cancer/Carcinogenesis-Tumor incidence in F1 offspring		
Duration and Exposure Route:	Inhalation-Gas-Duration: Acute (less than or equal to 24 hr)-F0- premating (6 hours)		
Species:	Mouse-CD-1 - [mouse]-Male		
Chemical:	1,3-Butadiene- Parent compound		
HERO ID:	5663561		
Domain	Metric	Rating	Comments
Domain 5: Exposure Methods Sensitivity			
Metric 6:	Chemical administration and characterization	Low	Limited details on the test substance were provided. The source (ICI plc) no longer exists, and the test substance purity was not provided. The performing laboratory did not independently verify the test substance. The test atmospheres were monitored for the presence of the dimer, but no data reporting analytical measurements of the test substance were provided. It is unclear whether the reported concentrations were target or nominal. The chambers were described as being closed and animals were exposed whole body. It was not explicitly stated whether the chambers were static or dynamic. The number of animals per cage was not specified. Storage of the test substance was reported and was appropriate. The metric is uninformative to do the lack of details of the inhalation chamber.
Metric 7:	Exposure timing, frequency, and duration	Uninformative	The exposure timing, frequency, and duration are not appropriate for assessing carcinogenicity.
Domain 6: Outcome Measures and Results Display			
Metric 8:	Endpoint sensitivity and specificity	Low	This study conducted a modified dominant lethality assay. The authors describe the study design as one that "straddles the fields of genetic, reproductive, and developmental toxicity". F1 offspring were examined for tumors (control and high exposure group only), no further methodological details were provided. The concentrations and concentration spacing were not explicitly justified. Only two groups were included, but current guidelines recommend 3. The animal species/strain and number of animals per group were adequate. The age and parity of females were not reported.
Metric 9:	Results presentation	Low	Only a qualitative statement specifying no differences in tumor incidences between controls and exposed animals was provided. Details of statistical methods were not included.

Overall Quality Determination**Uninformative**

Study Citation:	Anderson, D., Edwards, A. J., Brinkworth, M. H., Hughes, J. A. (1996). Male-mediated F1 effects in mice exposed to 1,3-butadiene. <i>Toxicology</i> 113(1-3):120-127.		
Health Outcome(s) and Reported Health Effect(s):	Other (please specify below) (Genotoxicity)-Karyotyping in F1 fetal livers		
Duration and Exposure Route:	Inhalation-Gas-Duration: Acute (less than or equal to 24 hr)-F0- premating (6 hours)		
Species:	Mouse-CD-1 - [mouse]-Male		
Chemical:	1,3-Butadiene- Parent compound		
HERO ID:	5663561		
Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	Low	All critical and some important information was reported. The test material was identified as 1,3-butadiene in the title and abstract. A source was specified. CD-1 mice (sex and source reported) were acutely exposed, whole body, to 0, 1250, or 6,250 ppm for 6 hours. The number of animals per group was reported. Missing information included the test substance purity, animal age, starting body weights, parity of unexposed females, and all animal husbandry details. A citation was provided for standard practices (an IARC book publication). Endpoint evaluation methods and qualitative or quantitative results for at least one endpoint were reported. The missing information is expected to reduce the ability to evaluate the study.
Domain 2: Selection and Performance			
	Metric 2: Allocation	Low	The study did not report how animals were allocated into study groups, or if animals were normalized to body weight.
	Metric 3: Observational Bias / Blinding Changes	Medium	No blinding was mentioned in the study; however, no endpoints were subjective or blinding is not required according to current guidelines.
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	Low	Negative controls were exposed to ambient air only. No quantitative data were provided, so it is unclear whether the negative control responses were appropriate. The study monitored dimer concentrations in the exposure atmosphere and reported a range from 3 to 133 ppm (results per group were not specified). It is unclear what impact the presence of the dimer may have had on the study results. Although positive controls are generally not required for reproductive/developmental studies, positive controls may have been appropriate for karyotyping. Other details to determine confounding (e.g., animal body weights, and husbandry conditions) were not reported. Additionally, reflex bradypnea was not assessed; however, the chemical is a respiratory irritant in humans but not in animals.
Domain 4: Selective Reporting and Attrition			
	Metric 5: Selective Reporting and Attrition	Uninformative	Mortality was not assessed or reported. It is unknown whether any exposed males died due to attrition, although it was indicated that the "majority of animals were in good health." Additionally, no quantitative data for the acute exposure experiment were reported, and for most outcomes, no sample sizes were specified. Due to the extensive omission of results, no comparisons across treatment groups can be conducted.

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Study Citation: Anderson, D., Edwards, A. J., Brinkworth, M. H., Hughes, J. A. (1996). Male-mediated F1 effects in mice exposed to 1,3-butadiene. *Toxicology* 113(1-3):120-127.

Health Outcome(s) and Reported Health Effect(s): Other (please specify below) (Genotoxicity)-Karyotyping in F1 fetal livers

Duration and Exposure Route: Inhalation-Gas-Duration: Acute (less than or equal to 24 hr)-F0- premating (6 hours)

Species: Mouse-CD-1 - [mouse]-Male

Chemical: 1,3-Butadiene- Parent compound

HERO ID: 5663561

Domain	Metric	Rating	Comments
Domain 5: Exposure Methods Sensitivity			
	Metric 6: Chemical administration and characterization	Low	Limited details on the test substance were provided. The source (ICI plc) no longer exists, and the test substance purity was not provided. The performing laboratory did not independently verify the test substance. The test atmospheres were monitored for the presence of the dimer, but no data reporting analytical measurements of the test substance were provided. It is unclear whether the reported concentrations were target or nominal. The chambers were described as being closed and animals were exposed whole body. It was not explicitly stated whether the chambers were static or dynamic. The number of animals per cage was not specified. Storage of the test substance was reported and was appropriate. The metric is uninformative to do the lack of details of the inhalation chamber.
	Metric 7: Exposure timing, frequency, and duration	Low	It is unclear whether the exposure, timing and frequency were appropriate for this outcome of interest.
Domain 6: Outcome Measures and Results Display			
	Metric 8: Endpoint sensitivity and specificity	Uninformative	No methodological details of the outcome assessment methods were provided including the number of fetuses examined. It is unclear if the methods used were consistent with standard practices for evaluating chromosome aberrations. The concentrations and concentration spacing were not explicitly justified. Only two groups were included. The animal species/strain and number of animals per group were adequate. The age and parity of females were not reported.
	Metric 9: Results presentation	Low	Only a qualitative statement indicating that all karyotypes were normal was provided.

Overall Quality Determination**Uninformative**

Study Citation:	Brinkworth, M. H., Anderson, D., Hughes, J. A., Jackson, L. I., Yu, T. W., Nieschlag, E. (1998). Genetic effects of 1,3-butadiene on the mouse testis. Mutation Research 397(1):67-75.		
Health Outcome(s) and Reported	Other (please specify below) (in vivo genotoxicity)-In testes: DNA damage (Comet assay) and unscheduled DNA synthesis (UDS)		
Health Effect(s):			
Duration and Exposure Route:	Inhalation-Gas-Duration: Acute (less than or equal to 24 hr)-6		
Species:	Mouse-CD-1 - [mouse]-Male		
Chemical:	1,3-Butadiene- Parent compound		
HERO ID:	4934798		
Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
Metric 1: Reporting Quality	Medium	All critical and most important information was provided. CD-1 mice (sex, source, and age were reported) were exposed to 1,3-butadiene (CASRN, source reported) via whole-body inhalation to the test material gas at 0, 12.5, or 125 ppm for a single 6 hr exposure (5/group). Most animal husbandry details (temperature, humidity, lighting, food and water availability) were specified. All endpoint evaluation methods were described. Quantitative results were reported for the endpoints of interest. The missing information included animal starting body weights, the number of animals per cage during exposure, and the purity of the test material.	
Domain 2: Selection and Performance			
Metric 2: Allocation	Medium	Males were randomly assigned to groups, but the method of randomization was not reported. It was not specified whether animals were normalized to body weights.	
Metric 3: Observational Bias / Blinding Changes	Medium	The study did not report blinding or other methods/procedures for reducing observational bias; however, the outcomes were not subjective in nature or used computerized image analysis and blinding was not required.	
Domain 3: Confounding / Variable Control			
Metric 4: Confounding / Variable Control	Uninformative	Some details to determine whether there was confounding between groups were missing. Animal body weights were not reported and respiration rate was not monitored in an inhalation study. However, the test material is considered to be a respiratory irritant in humans (PubChem), but not in animals. The study utilized an appropriate negative control (ambient air only). The negative control responses were appropriate. No positive controls were included. According to OECD TG 486, the guideline for an in vivo unscheduled DNA synthesis test, concurrent positive controls are required. Additionally, based on OECD TG 480 (in vivo mammalian Alkaline Comet assay), positive controls, or demonstration of proficiency from the performing laboratory is also required. The lack of positive controls in genotoxicity tests makes this study uninformative.	
Domain 4: Selective Reporting and Attrition			
Metric 5: Selective Reporting and Attrition	Low	It is unclear if any animal attrition occurred. There were five animals per group, but in some cases, data were provided for only 4 animals without further explanation. Sperm data were derived from the same number of sperm counts. Due to the small sample size, this could have a significant impact on the results.	

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Study Citation: Brinkworth, M. H., Anderson, D., Hughes, J. A., Jackson, L. I., Yu, T. W., Nieschlag, E. (1998). Genetic effects of 1,3-butadiene on the mouse testis. *Mutation Research* 397(1):67-75.

Health Outcome(s) and Reported Health Effect(s): Other (please specify below) (in vivo genotoxicity)-In testes: DNA damage (Comet assay) and unscheduled DNA synthesis (UDS)

Duration and Exposure Route: Inhalation-Gas-Duration: Acute (less than or equal to 24 hr)-6

Species: Mouse-CD-1 - [mouse]-Male

Chemical: 1,3-Butadiene- Parent compound

HERO ID: 4934798

Domain	Metric	Rating	Comments
Domain 5: Exposure Methods Sensitivity			
	Metric 6: Chemical administration and characterization	Low	The test material was obtained from Aldrich Chemical Company. The CASRN was specified, but purity was not reported. Due to the age of the study, the exact product purchased cannot be located on the supplier's website. The performing laboratory did not analytically verify the test substance or report that it was supplied with a certificate of analysis. The study methods referred to the test material as "BD", but the title of the paper specified it was 1,3-butadiene. The test material was stored at -20 degrees for long-term storage and at 4 degrees between exposures. Exposure atmospheres were generated by diluting the test substances (presumably as a gas) in a stream of dry air at a constant flow rate. Animals were exposed whole body, and the number of mice per chamber was not specified. It was not explicitly stated if the chambers were static or dynamic and it is not entirely clear based on the information provided and there was no mention of air changes. The target exposure concentrations were reported and justified by the authors; the lowest concentration is equivalent to the maximum permitted occupational exposure limit in several countries. The atmospheres were analytically monitored but no analytical values were provided. It was specified by the authors that concentrations within 15% of the target were considered acceptable. The missing details could have a significant impact on the study results.
	Metric 7: Exposure timing, frequency, and duration	Low	The exposure timing, frequency, and duration (single 6-hour inhalation exposure) were appropriate for the outcomes of interest and consistent with OECD guidelines.
Domain 6: Outcome Measures and Results Display			
	Metric 8: Endpoint sensitivity and specificity	Low	Some methodological details were provided. The study cited a previous publication (Anderson et al. 1997); this reference was not freely accessible at the time of this review. The OECD guideline for the in vivo Comet assay specifies that the test is not appropriate to measure DNA strand breaks in mature germ cells, and that a positive result in testis samples is not necessarily reflective of germ cell damage. The current study did the assay in sperm and saw a positive result. There is no specification on tissues in the OECD TG 489 for UDS assays, although they are typically done using liver tissue. Evaluations were conducted on all treatment groups. The animal model was appropriate, and animals were obtained from a commercial source. The sample size for the endpoints evaluated was sufficient for statistical analysis; however, the study indicated issues with high variability, particularly in the low-exposure group, which may have precluded the ability to detect a significant effect.
	Metric 9: Results presentation	High	Statistical methods were adequately described and data were presented as means \pm SD for all groups.

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Study Citation: Brinkworth, M. H., Anderson, D., Hughes, J. A., Jackson, L. I., Yu, T. W., Nieschlag, E. (1998). Genetic effects of 1,3-butadiene on the mouse testis. Mutation Research 397(1):67-75.

Health Outcome(s) and Reported Health Effect(s): Other (please specify below) (in vivo genotoxicity)-In testes: DNA damage (Comet assay) and unscheduled DNA synthesis (UDS)

Duration and Exposure Route: Inhalation-Gas-Duration: Acute (less than or equal to 24 hr)-6

Species: Mouse-CD-1 - [mouse]-Male

Chemical: 1,3-Butadiene- Parent compound

HERO ID: 4934798

Domain	Metric	Rating	Comments
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Overall Quality Determination

Uninformative

Study Citation:	Shugaev, B. B. (1969). Concentrations of hydrocarbons in tissues as a measure of toxicity. Archives of Environmental and Occupational Health 18(6):878-882.		
Health Outcome(s) and Reported Health Effect(s):	Mortality-LD50		
Duration and Exposure Route:	Inhalation-Gas-Duration: Acute (less than or equal to 24 hr)-4		
Species:	Rat-Not specified-Unknown		
Chemical:	1,3-Butadiene- Parent compound		
HERO ID:	62368		
Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
Metric 1: Reporting Quality		Uninformative	The animal species (mouse and rat), test material (butadiene), route (Inhalation), duration (4 hours), and a quantitative result (LD50) were reported. The exposure concentrations tested were not specified. The study provided none of the important information about the test chemical, animal model, husbandry, animals per group, or endpoint evaluation methods.
Domain 2: Selection and Performance			
Metric 2: Allocation		Medium	The study did not report how animals were allocated into groups.
Metric 3: Observational Bias / Blinding Changes		Medium	The study did not report use of blinding. Blinding is not typically required for acute toxicity assays.
Domain 3: Confounding / Variable Control			
Metric 4: Confounding / Variable Control		Medium	Negative and positive controls are not required for acute toxicity assays. No other information to determine possible confounding was provided.
Domain 4: Selective Reporting and Attrition			
Metric 5: Selective Reporting and Attrition		Medium	Results for the endpoint specified were provided. No other information was provided to support or dismiss the suggestion that there were differences among groups in animal attrition or health outcomes unrelated to exposure.
Domain 5: Exposure Methods Sensitivity			
Metric 6: Chemical administration and characterization		Low	Limited details were provided. The test chemical was identified as "butadiene" no further information (e.g., source, purity, CASRN etc.,) were provided. There is no indication that the test substance was analytically verified. The exposure concentrations were not specified. Animals were exposed in dynamic flow chambers, and the concentration of the test material was controlled by GC. However, no methods describing storage, or generation of the test substance were provided.
Metric 7: Exposure timing, frequency, and duration		High	The exposure timing, frequency, and duration (single 4-hr inhalation) are consistent with standard acute inhalation toxicity guidelines.
Domain 6: Outcome Measures and Results Display			

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Study Citation:	Shugaev, B. B. (1969). Concentrations of hydrocarbons in tissues as a measure of toxicity. Archives of Environmental and Occupational Health 18(6):878-882.
Health Outcome(s) and Reported Health Effect(s):	Mortality-LD50
Duration and Exposure Route:	Inhalation-Gas-Duration: Acute (less than or equal to 24 hr)-4
Species:	Rat-Not specified-Unknown
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	62368

Domain	Metric	Rating	Comments
	Metric 8: Endpoint sensitivity and specificity	Low	No guidelines or methods of outcome assessment were provided, but this study assessed lethality in an acute toxicity test. It was not specified how long the animals were observed. The concentrations tested, the number of groups, and the number of animals per group were not reported. It cannot be determined whether sampling was appropriate. The concentrations seemed sufficient for deriving an LD50. The species tested (mouse, rat) were standard, no other details on strain were provided.
	Metric 9: Results presentation	Medium	The study did not report how many animals died per group, or the timing or causes of death. Only LC50, as well as LC16 and LC84 values, were provided. Confidence limits were included. The statistical method used to calculate the LD50 was reported.

Overall Quality Determination**Low**

Study Citation:	Shugaev, B. B. (1969). Concentrations of hydrocarbons in tissues as a measure of toxicity. Archives of Environmental and Occupational Health 18(6):878-882.
Health Outcome(s) and Reported Health Effect(s):	Mortality-LD50
Duration and Exposure Route:	Inhalation-Gas-Duration: Acute (less than or equal to 24 hr)-2
Species:	Mouse-Not specified-Unknown
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	62368

Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	Uninformative	The animal species (mouse and rat), test material (butadiene), route (Inhalation), duration (4 hours), and a quantitative result (LD50) were reported. The exposure concentrations tested were not specified. The study provided none of the important information about the test chemical, animal model, husbandry, animals per group, or endpoint evaluation methods.
Domain 2: Selection and Performance			
	Metric 2: Allocation	Medium	The study did not report how animals were allocated into groups.
	Metric 3: Observational Bias / Blinding Changes	Medium	The study did not report use of blinding. Blinding is not typically required for acute toxicity assays.
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	Medium	Negative and positive controls are not required for acute toxicity assays. No other information to determine possible confounding was provided.
Domain 4: Selective Reporting and Attrition			
	Metric 5: Selective Reporting and Attrition	Medium	Results for the endpoint specified were provided. No other information was provided to support or dismiss the suggestion that there were differences among groups in animal attrition or health outcomes unrelated to exposure.
Domain 5: Exposure Methods Sensitivity			
	Metric 6: Chemical administration and characterization	Low	Limited details were provided. The test chemical was identified as "butadiene" no further information (e.g., source, purity, CASRN etc.,) were provided. There is no indication that the test substance was analytically verified. The exposure concentrations were not specified. Animals were exposed in dynamic flow chambers, and the concentration of the test material was controlled by GC. However, no methods describing storage, or generation of the test substance were provided.
	Metric 7: Exposure timing, frequency, and duration	High	The exposure timing, frequency, and duration (single 2-hr inhalation) are consistent with standard acute inhalation toxicity guidelines.
Domain 6: Outcome Measures and Results Display			

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Study Citation:	Shugaev, B. B. (1969). Concentrations of hydrocarbons in tissues as a measure of toxicity. Archives of Environmental and Occupational Health 18(6):878-882.
Health Outcome(s) and Reported Health Effect(s):	Mortality-LD50
Duration and Exposure Route:	Inhalation-Gas-Duration: Acute (less than or equal to 24 hr)-2
Species:	Mouse-Not specified-Unknown
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	62368

Domain	Metric	Rating	Comments
	Metric 8: Endpoint sensitivity and specificity	Low	No guidelines or methods of outcome assessment were provided, but this study assessed lethality in an acute toxicity test. It was not specified how long the animals were observed. The concentrations tested, the number of groups, and the number of animals per group were not reported. It cannot be determined whether sampling was appropriate. The concentrations seemed sufficient for deriving an LD50. The species tested (mouse, rat) were standard, no other details on strain were provided.
	Metric 9: Results presentation	Medium	The study did not report how many animals died per group, or the timing or causes of death. Only LC50, as well as LC16 and LC84 values, were provided. Confidence limits were included. The statistical method used to calculate the LD50 was reported.

Overall Quality Determination**Low**

Study Citation:	Hackett, P. L., Brown, M. G., Clark, M. L., Evanoff, J. J., Rowe, S. E., McClanahan, B. J., Buschbom, R. L., Decker, J. R., Rommereim, R. L., Westerberg, R. B. (1988). Sperm-head morphology study in B6C3F1 mice following inhalation exposure to 1,3-butadiene.		
Health Outcome(s) and Reported	Reproductive/Developmental-Male reproductive tract gross lesions, sperm morphology		
Health Effect(s):			
Duration and	Inhalation-Vapor-Duration: Short-term (>1-30 days)-6-5-day(s)		
Exposure Route:			
Species:	Mouse-B6C3F1 - [mouse]-Male		
Chemical:	1,3-Butadiene- Parent compound		
HERO ID:	62354		

Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	Medium	All critical information is reported. The authors report test substance identity, source, purity and lot number. Test animal species, strain, sex, source, starting age, approximate starting body weight and housing conditions (that included food and water availability, number of animals per cage, temperature and humidity) are reported. No description of a light/dark cycle is reported. Exposure methods are reported and endpoints with endpoint assessment methodology are all described.
Domain 2: Selection and Performance			
	Metric 2: Allocation	High	Animals were randomly assigned to groups via a computer program that randomized animals into groups based on body weight as a blocking factor. Ear tag numbers and toeclips were used to keep track of each animal.
	Metric 3: Observational Bias / Blinding Changes	High	Examiners were blinded to identity of the treatment groups for analysis of sperm morphology via labeling the slide with the animal number, which prevented the assessors from knowing which slide came from which group.
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	Medium	The authors included both a sham-air negative control and a positive control. There was no response in the negative control group, but there was also no significant difference for the positive control group, implying that the positive control was inadequate. Positive controls are normally not required for studies of male reproductive toxicity, and the assay did detect an effect with the test substance, so this lack of positive control response would only have a minor impact on the results. The authors measured other potentially confounding factors such as body weight, and confounding bias is not likely to impact the results. Food and water consumption were not measured but are not likely to impact the results for inhalation studies.
Domain 4: Selective Reporting and Attrition			
	Metric 5: Selective Reporting and Attrition	Medium	No attrition occurred during the study and most endpoints described in the methods are accounted for in the results. Gross lesions of the male reproductive tract were described as an endpoint in the abstract but were not mentioned in the methods nor results, and this omission is not explained.
Domain 5: Exposure Methods Sensitivity			

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Study Citation:	Hackett, P. L., Brown, M. G., Clark, M. L., Evanoff, J. J., Rowe, S. E., McClanahan, B. J., Buschbom, R. L., Decker, J. R., Rommereim, R. L., Westerberg, R. B. (1988). Sperm-head morphology study in B6C3F1 mice following inhalation exposure to 1,3-butadiene.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Male reproductive tract gross lesions, sperm morphology
Duration and Exposure Route:	Inhalation-Vapor-Duration: Short-term (>1-30 days)-6-5-day(s)
Species:	Mouse-B6C3F1 - [mouse]-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	62354

Domain	Metric	Rating	Comments
Metric 6:	Chemical administration and characterization	Medium	The authors performed independent analytical verification of the test substance identity, purity and exposure concentrations using an appropriate method. The authors identified potential impurities and took steps during the preparation, storage and handling of the test substance to minimize formation of this impurity. The inhalation exposure chamber is described, and the exposure methods were consistent between groups. Analytical, nominal and target concentrations are all stated. A minor concern is that a whole-body inhalation chamber was used but the number of air changes/hour was not stated.
Metric 7:	Exposure timing, frequency, and duration	Medium	The exposure frequency and duration were consistent between groups. The authors sacrificed animals 5 weeks after the last day of exposure, which was only for 5 consecutive days, which may potentially reduce the sensitivity of the endpoint assessment to detect results.

Domain 6: Outcome Measures and Results Display

Metric 8:	Endpoint sensitivity and specificity	Medium	There are no concerns regarding the species, sample size or concentration group spacing. While sperm morphology is a useful metric to detect male reproductive effects, the authors don't justify why they didn't report other metrics of sperm quality (such as motility or number). Other useful measures of male reproductive toxicity (such as histopathology) were not measured, which may have a minor impact on the ability of the study to address the intended outcomes of interest.
Metric 9:	Results presentation	High	The statistical methods were appropriate to address the outcomes of interest. Sperm morphology data is presented qualitatively in the results with measures of variance.

Overall Quality Determination**Medium**

Study Citation:	Hackett, P. L., Brown, M. G., Clark, M. L., Evanoff, J. J., Rowe, S. E., McClanahan, B. J., Buschbom, R. L., Decker, J. R., Rommereim, R. L., Westerberg, R. B. (1988). Sperm-head morphology study in B6C3F1 mice following inhalation exposure to 1,3-butadiene.		
Health Outcome(s) and Reported Health Effect(s):	Mortality-Death-Nutritional/Metabolic-Body weights, body weight gain %-Other (please specify below) (Clinical signs)-Clinical signs of toxicity		
Duration and Exposure Route:	Inhalation-Vapor-Duration: Short-term (>1-30 days)-6-5-day(s)		
Species:	Mouse-B6C3F1 - [mouse]-Male		
Chemical:	1,3-Butadiene- Parent compound		
HERO ID:	62354		

Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	Medium	All critical information is reported. The authors report test substance identity, source, purity and lot number. Test animal species, strain, sex, source, starting age, approximate starting body weight and housing conditions (that included food and water availability, number of animals per cage, temperature and humidity) are reported. No description of a light/dark cycle is reported. Exposure methods are reported and endpoints with endpoint assessment methodology are all described.
Domain 2: Selection and Performance			
	Metric 2: Allocation	High	Animals were randomly assigned to groups via a computer program that randomized animals into groups based on body weight as a blocking factor. Ear tag numbers and toeclips were used to keep track of each animal.
	Metric 3: Observational Bias / Blinding Changes	Medium	While the animals were assigned metal tags and toe clips to keep track of their identity, it is not stated whether investigators were blinded to treatment groups when examining animals for mortality and body weights. Regardless, these endpoints would not be susceptible to observational bias.
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	Medium	The authors included both a sham-air negative control and a positive control. There was no response in the negative control, and the positive control did have a response for body weights. Positive controls are normally not required for this type of study. Food and water consumption were not measured but are not likely to impact the results for inhalation studies and confounding bias is unlikely.
Domain 4: Selective Reporting and Attrition			
	Metric 5: Selective Reporting and Attrition	High	No attrition occurred during the study and all endpoints described in the methods are accounted for in the results.
Domain 5: Exposure Methods Sensitivity			
	Metric 6: Chemical administration and characterization	Medium	The authors performed independent analytical verification of the test substance identity, purity and exposure concentrations using an appropriate method. The authors identified potential impurities and took steps during the preparation, storage and handling of the test substance to minimize formation of this impurity. The inhalation exposure chamber is described, and the exposure methods were consistent between groups. Analytical, nominal and target concentrations are all stated. A minor concern is that a whole-body inhalation chamber was used but the number of air changes/hour was not stated.

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Study Citation:	Hackett, P. L., Brown, M. G., Clark, M. L., Evanoff, J. J., Rowe, S. E., McClanahan, B. J., Buschbom, R. L., Decker, J. R., Rommereim, R. L., Westerberg, R. B. (1988). Sperm-head morphology study in B6C3F1 mice following inhalation exposure to 1,3-butadiene.
Health Outcome(s) and Reported Health Effect(s):	Mortality-Death-Nutritional/Metabolic-Body weights, body weight gain %-Other (please specify below) (Clinical signs)-Clinical signs of toxicity
Duration and Exposure Route:	Inhalation-Vapor-Duration: Short-term (>1-30 days)-6-5-day(s)
Species:	Mouse-B6C3F1 - [mouse]-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	62354

Domain	Metric	Rating	Comments
Metric 7:	Exposure timing, frequency, and duration	Medium	The exposure frequency and duration were consistent between groups. The authors sacrificed animals 5 weeks after the last day of exposure, which may potentially reduce the sensitivity of the endpoint assessment to detect results.

Domain 6: Outcome Measures and Results Display

Metric 8:	Endpoint sensitivity and specificity	High	There are no concerns regarding the species, sample size or concentration group spacing, and the measured endpoints fully addressed the intended outcomes of interest. While no effects on mortality or body weight were observed, these may be considered control effects.
Metric 9:	Results presentation	Medium	The statistical methods were appropriate to address the outcomes of interest. Data are presented quantitatively in the results but body weight gain % data does not include measured of variance.

Overall Quality Determination**Medium**

Study Citation:	I-D, Adler, Filser, J., Gonda, H., Schriever-Schwemmer, G. (1998). Dose response study for 1,3-butadiene-induced dominant lethal mutations and heritable translocations in germs cells of male mice. <i>Mutation Research</i> 397(1):85-92.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Percentage of pregnant females, number of total implants, live implants, and dead implants in dominant lethal study.Litter size at birth and at weaning for translocation assay.
Duration and Exposure Route:	Inhalation-Vapor-Duration: Short-term (>1-30 days)-F0- premating-F0- premating (5)
Species:	Mouse-Other (102/E1 X C3H/E1)-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	5663591

Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	Medium	The test substance was identified as 1,3-Butadiene. The source (Linde, Unterschleisheim, Germany) and purity (99.5%) were reported. Test animal species, strain, and sex were reported. Age and initial body weights were not reported for all sexes and outcomes. The animals were obtained from laboratory-maintained animal colony. Husbandry conditions are partially reported. Animals were kept in a light and temperature-controlled rooms (details not provided). Food and water were available ad libitum. The dose levels, frequency, duration, and route of exposure were reported. The target concentrations were reported. Actual concentrations were reported to be within 6% of nominal concentration (data not shown). Endpoint evaluation methods were reported along with quantitative data. All critical information is provided and although some important information is missing, the missing information is not expected to significantly impact the study evaluation.
Domain 2: Selection and Performance			
	Metric 2: Allocation	Low	Study does not report how animals were allocated to study groups.
	Metric 3: Observational Bias / Blinding Changes	Medium	Blinding or other measures to reduce observational bias were not reported; however, the endpoints are not subjective in nature (counts).
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	Medium	A sham-exposed negative control group was included. Husbandry conditions, body weight, and food and water intake were not fully reported therefore potential confounding could not be determined. Respiratory rate was not reported but the chemical is not expected to be a respiratory irritant. A positive control was not included; not a concern because a (mild) positive effect was observed and this laboratory has shown positive responses within the last 5 years.
Domain 4: Selective Reporting and Attrition			
	Metric 5: Selective Reporting and Attrition	Medium	Mortality was not reported. Fifty males/group were treated and mated with females, it is not reported if any males failed to mate successfully with female and were removed from study.
Domain 5: Exposure Methods Sensitivity			

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Study Citation:	I-D, Adler, Filser, J., Gonda, H., Schriever-Schwemmer, G. (1998). Dose response study for 1,3-butadiene-induced dominant lethal mutations and heritable translocations in germs cells of male mice. <i>Mutation Research</i> 397(1):85-92.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Percentage of pregnant females, number of total implants, live implants, and dead implants in dominant lethal study. Litter size at birth and at weaning for translocation assay.
Duration and Exposure Route:	Inhalation-Vapor-Duration: Short-term (>1-30 days)-F0- premating-F0- premating (5)
Species:	Mouse-Other (102/E1 X C3H/E1)-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	5663591

Domain	Metric	Rating	Comments
Metric 6:	Chemical administration and characterization	Low	The source and purity (99.5%) of the test substance were reported. Target concentrations were reported. Chamber concentrations were measured every 15 minutes during the first hour of exposure and at 30-minute intervals thereafter. Study authors report that the chamber concentrations did not deviate more than 6% from the nominal concentration (data not shown). The generation of test substance vapor was reported minimal details. Storage of test substance was not reported. Animals were exposed in a whole-body dynamic inhalation chamber. Since test substance may deposit on the fur for the animal during exposure and they may ingest the test substance during grooming, the study was downgraded. The number of air changes/hour was not reported.
Metric 7:	Exposure timing, frequency, and duration	Medium	In this inhalation study, the route and frequency were appropriate for the study's purpose, although given the mild response it is possible that longer exposure time may have increased response by capturing a larger range of spermatogenesis.

Domain 6: Outcome Measures and Results Display

Metric 8:	Endpoint sensitivity and specificity	High	According to OECD guidelines 478 (Rodent Dominant Lethal Test) pregnant females should be sacrificed in the second half of pregnancy at gestation day 13. This study sacrificed females at GD 14-16 which is slightly longer than the recommended, but still within the second half of pregnancy. The number of animals/group was appropriate. The outcome methodology was sensitive to outcome of interest. Animals were assessed consistently across study groups. Animals were obtained from a laboratory-maintained colony and were appropriate for the study type.
Metric 9:	Results presentation	Low	Data are presented in Table format. Statistic was performed on number of dead implants/female only. Data were not presented in such a way that independent statistic could be performed on some endpoints (SE not provided). Additionally, sex ratio not reported. Table and accompanying graph were difficult to interpret.

Overall Quality Determination

Medium

Study Citation:	I-D, Adler, Filser, J., Gonda, H., Schriever-Schwemmer, G. (1998). Dose response study for 1,3-butadiene-induced dominant lethal mutations and heritable translocations in germs cells of male mice. <i>Mutation Research</i> 397(1):85-92.
Health Outcome(s) and Reported Health Effect(s):	Other (please specify below) (Dominant lethality)-Dominant lethality
Duration and Exposure Route:	Inhalation-Vapor-Duration: Short-term (>1-30 days)-F0- premating-F0- premating (5)
Species:	Mouse-Other (102/E1 X C3H/E1)-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	5663591

Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	Medium	The test substance was identified as 1,3-Butadiene. The source (Linde, Unterschleisheim, Germany) and purity (99.5%) were reported. Test animal species, strain, and sex were reported. Age and initial body weights were not reported. The animals were obtained from laboratory-maintained animal colony. Husbandry conditions are partially reported. Animals were kept in a light and temperature-controlled rooms (details not provided). Food and water were available ad libitum. The dose levels, frequency, duration, and route of exposure were reported. The target concentrations were reported. Actual concentrations were reported to be within 6% of nominal concentration (data not shown). Endpoint evaluation methods were reported along with quantitative data. All critical information is provided and although some important information is missing, the missing information is not expected to significantly impact the study evaluation.
Domain 2: Selection and Performance			
	Metric 2: Allocation	Low	Study does not report how animals were allocated to study groups.
	Metric 3: Observational Bias / Blinding Changes	Medium	Blinding or other measures to reduce observational bias were not reported; however, the endpoints are either not subjective in nature (counts).
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	Medium	A sham-exposed negative control group was included. Husbandry conditions, body weight, and food and water intake were not fully reported therefore potential confounding could not be determined. Respiratory rate was not reported but the chemical is not expected to be a respiratory irritant. A positive control was not included however a positive response was obtained in this experiment and this laboratory has shown positive responses within the last 5 years.
Domain 4: Selective Reporting and Attrition			
	Metric 5: Selective Reporting and Attrition	Medium	Mortality was not reported. Fifty males/group were treated and mated with females, it is not reported if any males failed to mate successfully with female and were removed from study.
Domain 5: Exposure Methods Sensitivity			

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Study Citation:	I-D, Adler, Filser, J., Gonda, H., Schriever-Schwemmer, G. (1998). Dose response study for 1,3-butadiene-induced dominant lethal mutations and heritable translocations in germs cells of male mice. <i>Mutation Research</i> 397(1):85-92.
Health Outcome(s) and Reported Health Effect(s):	Other (please specify below) (Dominant lethality)-Dominant lethality
Duration and Exposure Route:	Inhalation-Vapor-Duration: Short-term (>1-30 days)-F0- premating-F0- premating (5)
Species:	Mouse-Other (102/E1 X C3H/E1)-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	5663591

Domain	Metric	Rating	Comments
Metric 6:	Chemical administration and characterization	Low	The source and purity (99.5%) of the test substance were reported. Target concentrations were reported. Chamber concentrations were measured every 15 minutes during the first hour of exposure and at 30-minute intervals thereafter. Study authors report that the chamber concentrations did not deviate more than 6% from the nominal concentration (data not shown). The generation of test substance vapor was reported minimal details. Storage of test substance was not reported. Animals were exposed in a whole-body dynamic inhalation chamber. Since test substance may deposit on the fur for the animal during exposure and they may ingest the test substance during grooming, the study was downgraded. The number of air changes/hour was not reported.
Metric 7:	Exposure timing, frequency, and duration	Medium	In this inhalation study, the route and frequency were appropriate for the study's purpose, although given the mild response it is possible that longer exposure time may have increased response by capturing a larger range of spermatogenesis.

Domain 6: Outcome Measures and Results Display

Metric 8:	Endpoint sensitivity and specificity	High	According to OECD guidelines 478 (Rodent Dominant Lethal Test) pregnant females should be sacrificed in the second half of pregnancy at gestation day 13. This study sacrificed females at GD 14-16 which is slightly longer than the recommended, but still within the second half of pregnancy. The number of animals/group was appropriate. The outcome methodology was sensitive to outcome of interest. Animals were assessed consistently across study groups. Animals were obtained from a laboratory-maintained colony and were appropriate for the study type.
Metric 9:	Results presentation	Low	Dominant lethality data was not analyzed using the methods outlined in OECD guidelines. OECD guidelines calculate dominant lethality as (post-implantation deaths/total implantation per female) x 100, this differs from calculations study authors used: %DL = [1 - (live implants per female in the experimental group / live implants per female in the control group)] X 100. However, data are reported so that DL could be calculated independently. Also, guidelines suggest statistical tests used should consider the male animal as the experimental unit, this was not done by study authors. Table and accompanying graph were difficult to interpret.

Overall Quality Determination

Medium

Study Citation:	I-D, Adler, Filser, J., Gonda, H., Schriever-Schwemmer, G. (1998). Dose response study for 1,3-butadiene-induced dominant lethal mutations and heritable translocations in germs cells of male mice. <i>Mutation Research</i> 397(1):85-92.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Percentage of pregnant females, number of total implants, live implants, and dead implants in dominant lethal study. Litter size at birth and at weaning for translocation assay.
Duration and Exposure Route:	Inhalation-Vapor-Duration: Short-term (>1-30 days)-F0- premating-F0- premating (5)
Species:	Mouse-Other (C3H/E1)-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	5663591

Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	Medium	The test substance was identified as 1,3-Butadiene. The source (Linde, Unterschleisheim, Germany) and purity (99.5%) were reported. Test animal species, strain, and sex were reported. Age and initial body weights were not reported. The animals were obtained from laboratory-maintained animal colony. Husbandry conditions are partially reported. Animals were kept in a light and temperature-controlled rooms (details not provided). Food and water were available ad libitum. The dose levels, frequency, duration, and route of exposure were reported. The target concentrations were reported. Actual concentrations were reported to be within 6% of nominal concentration (data not shown). Endpoint evaluation methods were reported along with quantitative data. All critical information is provided and although some important information is missing, the missing information is not expected to significantly impact the study evaluation.
Domain 2: Selection and Performance			
	Metric 2: Allocation	Low	Study does not report how animals were allocated to study groups.
	Metric 3: Observational Bias / Blinding Changes	Medium	Blinding or other measures to reduce observational bias were not reported; however, the endpoints are either not subjective in nature (counts).
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	Medium	A sham-exposed negative control group was included. Husbandry conditions, body weight, and food and water intake were not fully reported for all sexes and outcomes, therefore potential confounding could not be determined. Respiratory rate was not reported but the chemical is not expected to be a respiratory irritant. A positive control was not included however a positive response was obtained in this experiment and this laboratory has shown positive responses within the last 5 years.
Domain 4: Selective Reporting and Attrition			
	Metric 5: Selective Reporting and Attrition	Medium	The study did not report mortality. It is unclear if all males successfully mated with females.
Domain 5: Exposure Methods Sensitivity			

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Study Citation:	I-D, Adler, Filser, J., Gonda, H., Schriever-Schwemmer, G. (1998). Dose response study for 1,3-butadiene-induced dominant lethal mutations and heritable translocations in germs cells of male mice. <i>Mutation Research</i> 397(1):85-92.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Percentage of pregnant females, number of total implants, live implants, and dead implants in dominant lethal study. Litter size at birth and at weaning for translocation assay.
Duration and Exposure Route:	Inhalation-Vapor-Duration: Short-term (>1-30 days)-F0- premating-F0- premating (5)
Species:	Mouse-Other (C3H/E1)-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	5663591

Domain	Metric	Rating	Comments
Metric 6:	Chemical administration and characterization	Low	The source and purity (99.5%) of the test substance were reported. Target concentrations were reported. Chamber concentrations were measured every 15 minutes during the first hour of exposure and at 30-minute intervals thereafter. Study authors report that the chamber concentrations did not deviate more than 6% from the nominal concentration (data not shown). The generation of test substance vapor was reported minimal details. Storage of test substance was not reported. Animals were exposed in a whole-body dynamic inhalation chamber. Since test substance may deposit on the fur for the animal during exposure and they may ingest the test substance during grooming, the study was downgraded. The number of air changes/hour was not reported.
Metric 7:	Exposure timing, frequency, and duration	Medium	In this inhalation study, the route and frequency were appropriate for the study's purpose, although given the mild response it is possible that longer exposure time may have increased response by capturing a larger range of spermatogenesis.

Domain 6: Outcome Measures and Results Display

Metric 8:	Endpoint sensitivity and specificity	High	According to OECD guidelines 478 (Rodent Dominant Lethal Test) pregnant females should be sacrificed in the second half of pregnancy at gestation day 13. This study sacrificed females at GD 14-16 which is slightly longer than the recommended, but still within the second half of pregnancy. The number of animals/group was appropriate. The outcome methodology was sensitive to outcome of interest. Animals were assessed consistently across study groups. Animals were obtained from a laboratory-maintained colony and were appropriate for the study type.
Metric 9:	Results presentation	Low	Data are presented in Table format. Statistic was performed on number of dead implants/female only. Data were not presented in such a way that independent statistic could be performed on some endpoints (SE not provided). Additionally, sex ratio not reported. Table and accompanying graph were difficult to interpret.

Overall Quality Determination

Medium

Study Citation:	I-D, Adler, Filser, J., Gonda, H., Schriever-Schwemmer, G. (1998). Dose response study for 1,3-butadiene-induced dominant lethal mutations and heritable translocations in germs cells of male mice. <i>Mutation Research</i> 397(1):85-92.		
Health Outcome(s) and Reported Health Effect(s):	Other (please specify below) (Genotoxicity)-Translocation assay		
Duration and Exposure Route:	Inhalation-Vapor-Duration: Short-term (>1-30 days)-F0- premating-F0- premating (5)		
Species:	Mouse-Other (C3H/E1)-Male		
Chemical:	1,3-Butadiene- Parent compound		
HERO ID:	5663591		
Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	Medium	The test substance was identified as 1,3-Butadiene. The source (Linde, Unterschleissheim, Germany) and purity (99.5%) were reported. Test animal species, strain, and sex were reported. Age and initial body weights were not reported. The animals were obtained from laboratory-maintained animal colony. Husbandry conditions are partially reported. Animals were kept in a light and temperature-controlled rooms (details not provided). Food and water were available ad libitum. The dose levels, frequency, duration, and route of exposure were reported. The target concentrations were reported. Actual concentrations were reported to be within 6% of nominal concentration (data not shown). Endpoint evaluation methods were reported along with quantitative data. All critical information is provided and although some important information is missing, the missing information is not expected to significantly impact the study evaluation.
Domain 2: Selection and Performance			
	Metric 2: Allocation	Low	Study does not report how animals were allocated to study groups.
	Metric 3: Observational Bias / Blinding Changes	Medium	Blinding or other measures to reduce observational bias were not reported; however, the endpoints are either not subjective in nature.
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	Uninformative	A sham-exposed negative control group was included. Husbandry conditions, body weight, and food and water intake were not fully reported therefore potential confounding could not be determined. Respiratory rate was not reported but the chemical is not expected to be a respiratory irritant. A positive control shown in a graph but without any description. It is not clear if this was part of the current study or historical data - less important because a positive response was obtained in this experiment. The study is deemed unacceptable because a concurrent negative control was not used for analysis. The study compares data to historic controls but does not provide any information on the study in which these data were obtained from.
Domain 4: Selective Reporting and Attrition			
	Metric 5: Selective Reporting and Attrition	Medium	The study did not report mortality. It is unclear if all males successfully mated with females.
Domain 5: Exposure Methods Sensitivity			

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Study Citation: I-D, Adler, Filser, J., Gonda, H., Schriever-Schwemmer, G. (1998). Dose response study for 1,3-butadiene-induced dominant lethal mutations and heritable translocations in germs cells of male mice. *Mutation Research* 397(1):85-92.

Health Outcome(s) and Reported Health Effect(s): Other (please specify below) (Genotoxicity)-Translocation assay

Duration and Exposure Route: Inhalation-Vapor-Duration: Short-term (>1-30 days)-F0- premating-F0- premating (5)

Species: Mouse-Other (C3H/E1)-Male
Chemical: 1,3-Butadiene- Parent compound

HERO ID: 5663591

Domain	Metric	Rating	Comments
	Metric 6: Chemical administration and characterization	Medium	The source and purity (99.5%) of the test substance were reported. Target concentrations were reported. Chamber concentrations were measured every 15 minutes during the first hour of exposure and at 30-minute intervals thereafter. Study authors report that the chamber concentrations did not deviate more than 6% from the nominal concentration (data not shown). The generation of test substance vapor was reported minimal details. Storage of test substance was not reported. Animals were exposed in a whole-body dynamic inhalation chamber. Since test substance may deposit on the fur for the animal during exposure and they may ingest the test substance during grooming, the study was downgraded. The number of air changes/hour was not reported.
	Metric 7: Exposure timing, frequency, and duration	Medium	In this inhalation study, the route and frequency were appropriate for the study's purpose, but longer exposure may have covered a wider range of spermatogenesis.

Domain 6: Outcome Measures and Results Display

Metric 8: Endpoint sensitivity and specificity	Medium	The outcome methodology was sensitive to outcome of interest. According to OECD guidelines 485, about 500 F1 offspring should be assessed for translocation assay. This study examined 434 animals; this is slightly less than recommended. Animals were assessed consistently across study groups. Animals were obtained from a laboratory-maintained colony and were appropriate for the study type.
Metric 9: Results presentation	Low	Data is reported and statistical analysis was performed using historical control data (details on historical control experiment not provided).

Overall Quality Determination

Uninformative

Study Citation:	Lee, J. H., Kang, H. S., Han, D. H. (2005). Ratios of N-(2,3,4-trihydroxybutyl) valine and N-(2-hydroxy-3-butenyl) valine formed hemoglobin adducts in female mice inhalation exposure with 1,3-butadiene. <i>Toxicology and Industrial Health</i> 21(1):15-20.
Health Outcome(s) and Reported	Nutritional/Metabolic-Body weight
Health Effect(s):	
Duration and Exposure Route:	Inhalation-Vapor-Duration: Short-term (>1-30 days)-5-5-3-week(s)
Species:	Mouse-ICR - [mouse]-Female
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	1329207

Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	Medium	The test substance was identified as 1,3-Butadiene. The source was reported (Sigma, St. Louis, MO). Purity was not reported; however, Sigma's website reports the purity as ≥99%. Test animal species, strain, sex, source, and initial body weight were reported. Age of the mice was not reported. Husbandry conditions (temperature, humidity, and light cycle) were reported. The number of animals/cage was not reported. Food and water were available ad libitum. The dose levels, frequency, duration, and route of exposure were reported. The nominal concentrations were reported. Concentration of test substance in the inhalation chamber were not reported. Endpoint evaluation methods were reported along with quantitative data. All critical information is provided and although some important information is missing, the missing information is not expected to significantly impact the study evaluation.
Domain 2: Selection and Performance			
	Metric 2: Allocation	High	Animals were randomly assigned to groups based on initial body weights.
	Metric 3: Observational Bias / Blinding Changes	Medium	Blinding or other measures to reduce observational bias were not reported; however, the endpoint evaluated was not subjective in nature (body weight) therefore lack of blinding is unlikely to substantially impact results.
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	Medium	Body weight was reported; however, food intake and water intake were not. Husbandry conditions were adequate; slight variations are not expected to substantially effect results. A negative control group was included however it is unclear if the animals were sham treated. The response of the negative controls was appropriate. Respiratory rate was not reported but the chemical is not expected to be a respiratory irritant.
Domain 4: Selective Reporting and Attrition			
	Metric 5: Selective Reporting and Attrition	High	The study does not report if any animals died during the study. Body weight data are reported as means +/- SE; the number of animals are stated as 15 per group. The number of exposed animals is reported; however, it is unclear if all exposed animals were included in analysis (but can be assumed).
Domain 5: Exposure Methods Sensitivity			

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Study Citation:	Lee, J. H., Kang, H. S., Han, D. H. (2005). Ratios of N-(2,3,4-trihydroxybutyl) valine and N-(2-hydroxy-3-butenyl) valine formed hemoglobin adducts in female mice inhalation exposure with 1,3-butadiene. <i>Toxicology and Industrial Health</i> 21(1):15-20.
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Body weight
Duration and Exposure Route:	Inhalation-Vapor-Duration: Short-term (>1-30 days)-5-5-3-week(s)
Species:	Mouse-ICR - [mouse]-Female
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	1329207

Domain	Metric	Rating	Comments
Metric 6:	Chemical administration and characterization	Low	The source of the test substance was reported; purity was not however the manufacturer's website reports purity as $\geq 99\%$. Only nominal concentrations are reported. The study did not measure or report actual concentrations. Generation of test substance vapor was reported with minimal details. A dynamic whole body inhalation chamber was used with only 5-7 air changes per hour. This is less than the recommended ≥ 10 air changes/hour.
Metric 7:	Exposure timing, frequency, and duration	High	In this inhalation study, the route, frequency, and duration of exposure (5 hours/day, 5 days/week up to 3 weeks) were appropriate for the study type and outcomes of interest.

Domain 6: Outcome Measures and Results Display

Metric 8:	Endpoint sensitivity and specificity	Medium	Outcome methodologies were sensitive to outcome of interest. Test animals were obtained from a commercial source. The number of animals/group was appropriate. Animals were assessed consistently across study groups. Two concentrations were studied. The study did not report reasoning for choosing these concentrations. A NOAEL could not be determined, but the number of exposure groups and spacing of exposure levels were adequate to show results relevant to the outcome of interest (dose-response relationship).
Metric 9:	Results presentation	Medium	Data were reported as means \pm SE. Statistics were performed by study authors, but they did not report which tests were run, only indicated significant differences. The number of animals included for calculation of the means was not reported, therefore independent statistical analysis cannot be performed.

Overall Quality Determination**Medium**

Study Citation:	LRRI, (2005). [Redacted] 1,3-Butadiene: Whole-body inhalation exposure of rats and mice.		
Health Outcome(s) and Reported	Mortality-Mortality-Other (please specify below) (Clinical signs)-Clinical signs of toxicity or abnormalities		
Health Effect(s):			
Duration and Exposure Route:	Inhalation-Vapor-Duration: Short-term (>1-30 days)-5-6-4-week(s)		
Species:	Rat-Sprague-Dawley - [rat]-Both-Mouse-B6C3F1 - [mouse]-Both		
Chemical:	1,3-Butadiene- Parent compound		
HERO ID:	11273463		
Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
Metric 1: Reporting Quality		Medium	The test substance was identified as 1,3-Butadiene. The source (Matheson) and purity were reported. Test animal species, strain, sex, age, source and initial body weights were reported. Husbandry conditions were maintained in accordance with recommendations in The Guide for Care and Use of Laboratory Animals (temperature [20-26oC] and humidity were monitored). The number of animals/cage was not reported. Food and water were available ad libitum. The dose levels, frequency, duration, and route of exposure were reported. The target and actual concentrations were reported. Endpoint evaluation methods were reported along with negative findings in text (no data are shown). All critical information is provided and although some important information is missing, the missing information is not expected to significantly impact the study evaluation.
Domain 2: Selection and Performance			
Metric 2: Allocation		High	Animals were randomly assigned to study groups by weight using computerized data acquisition system.
Metric 3: Observational Bias / Blinding Changes		Medium	Blinding or other measures to reduce observational bias were not reported; however, the endpoints are either not subjective (mortality, body weight) or clinical signs.
Domain 3: Confounding / Variable Control			
Metric 4: Confounding / Variable Control		Medium	A sham-exposed negative control group was included. Study reports that no deviation in environmental conditions were seen. Mean initial body weights were comparable to controls. Body weight, food and water intake were not reported, the impact of these potential confounding variables cannot be determined. Respiratory rate was not reported but the chemical is not expected to be a respiratory irritant. The study did not report all information to determine confounding but the impact on results is expected to be minimal and reported information did not identify differences among study groups.
Domain 4: Selective Reporting and Attrition			
Metric 5: Selective Reporting and Attrition		High	The study reports no animals were moribund or died.
Domain 5: Exposure Methods Sensitivity			
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Study Citation:	LRRI, (2005). [Redacted] 1,3-Butadiene: Whole-body inhalation exposure of rats and mice.
Health Outcome(s) and Reported Health Effect(s):	Mortality-Mortality-Other (please specify below) (Clinical signs)-Clinical signs of toxicity or abnormalities
Duration and Exposure Route:	Inhalation-Vapor-Duration: Short-term (>1-30 days)-5-6-4-week(s)
Species:	Rat-Sprague-Dawley - [rat]-Both-Mouse-B6C3F1 - [mouse]-Both
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	11273463

Domain	Metric	Rating	Comments
Metric 6:	Chemical administration and characterization	Medium	The source (Matheson) and purity (>99%) of the test substance were reported. Target and actual concentrations were reported with variance. The average concentrations were within 1% of the target. Generation of test substance vapor was adequately reported. Animals were exposed in a whole-body dynamic inhalation chamber with 12-15 air change/hour. Since test substance may deposit on the fur the animal during exposure and they may ingest the test substance during grooming, the study was downgraded to medium.
Metric 7:	Exposure timing, frequency, and duration	Medium	In this inhalation study, the route, frequency, and duration were appropriate for the study's aim, but no results were observed and a longer duration may have resulted in more sensitive findings.

Domain 6: Outcome Measures and Results Display

Metric 8:	Endpoint sensitivity and specificity	Low	The number of animals is not clearly reported. The study reports 160 animals will be used for exposure. It is unclear if this is 160/sex (40/sex/group) or 160 total animals (20/sex/group). Methodologies to assess mortality and clinical signs were appropriate, but additional higher doses would have been more appropriate for identifying a threshold response.
Metric 9:	Results presentation	Medium	Findings are reported as negative in text.

Overall Quality Determination

Medium

Study Citation:	LRRI, (2005). [Redacted] 1,3-Butadiene: Whole-body inhalation exposure of rats and mice.
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Body weight
Duration and Exposure Route:	Inhalation-Vapor-Duration: Short-term (>1-30 days)-5-6-4-week(s)
Species:	Rat-Sprague-Dawley - [rat]-Both-Mouse-B6C3F1 - [mouse]-Both
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	11273463

Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	Medium	The test substance was identified as 1,3-Butadiene. The source (Matheson) and purity were reported. Test animal species, strain, sex, age, source and initial body weights were reported. Husbandry conditions were maintained in accordance with recommendations in The Guide for Care and Use of Laboratory Animals (temperature [20-26°C] and humidity were monitored). The number of animals/cage was not reported. Food and water were available ad libitum. The dose levels, frequency, duration, and route of exposure were reported. The target and actual concentrations were reported. Endpoint evaluation methods were reported along with negative findings in text (no data are shown). All critical information is provided and although some important information is missing, the missing information is not expected to significantly impact the study evaluation.
Domain 2: Selection and Performance			
	Metric 2: Allocation	High	Animals were randomly assigned to study groups by weight using computerized data acquisition system.
	Metric 3: Observational Bias / Blinding Changes	Medium	Blinding or other measures to reduce observational bias were not reported; however, the endpoints are either not subjective (mortality, body weight) or clinical signs.
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	Medium	A sham-exposed negative control group was included. Study reports that no deviation in environmental conditions were seen. Mean initial body weights were comparable to controls. Body weight, food and water intake were not reported, the impact of these potential confounding variables cannot be determined. Respiratory rate was not reported but the chemical is not expected to be a respiratory irritant. The study did not report all information to determine confounding but the impact on results is expected to be minimal and reported information did not identify differences among study groups.
Domain 4: Selective Reporting and Attrition			
	Metric 5: Selective Reporting and Attrition	High	The study reports no animals were moribund or died.
Domain 5: Exposure Methods Sensitivity			
	Metric 6: Chemical administration and characterization	Medium	The source and purity (>99%) of the test substance were reported. Target and actual concentrations were reported with variance. The average concentrations were within 1% of the target. Generation of test substance vapor was adequately reported. Animals were exposed in a whole-body dynamic inhalation chamber with 12-15 air change/hour. Since test substance may deposit on the fur of the animal during exposure and they may ingest the test substance during grooming, the study was downgraded to medium.

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Study Citation: LRRI, (2005). [Redacted] 1,3-Butadiene: Whole-body inhalation exposure of rats and mice.
Health Outcome(s) and Reported Health Effect(s): Nutritional/Metabolic-Body weight
Duration and Exposure Route: Inhalation-Vapor-Duration: Short-term (>1-30 days)-5-6-4-week(s)
Species: Rat-Sprague-Dawley - [rat]-Both-Mouse-B6C3F1 - [mouse]-Both
Chemical: 1,3-Butadiene- Parent compound
HERO ID: 11273463

Domain	Metric	Rating	Comments
	Metric 7: Exposure timing, frequency, and duration	Medium	In this inhalation study, the route, frequency, and duration were appropriate for the study's aim, but since no effects were observed a longer duration would have been more sensitive.

Domain 6: Outcome Measures and Results Display

Metric 8: Endpoint sensitivity and specificity	Low	The number of animals is not clearly reported. The study reports 160 animals will be used for exposure. It is unclear if this is 160/sex (40/sex/group) or 160 total animals (20/sex/group). Methodologies to assess mortality and clinical signs were appropriate, but additional higher doses would have been more appropriate for identifying a threshold response.
Metric 9: Results presentation	Uninformative	The study only reports initial body weights. It is unclear if this study was only intended to be a preliminary study or an incomplete report.

Overall Quality Determination

Uninformative

Study Citation:	National Institutes of Health, Services, D.o. (1984). Toxicology and carcinogenesis studies of 1,3-butadiene (CAS no. 106-99-0) in B6C3F1 mice (inhalation studies). 288:1-111.
Health Outcome(s) and Reported Health Effect(s):	Mortality-Survival/mortality-Skin/Connective Tissue-Necropsy and histopathology of skin and gross lesions-Immune/Hematological-Necropsy and histopathology of mandibular lymph node, mesenteric lymph node, spleen, thymus, and gross lesions-Reproductive/Developmental-Necropsy and histopathology of mammary gland, seminal vesicles, prostate, testes, ovaries, uterus, and gross lesions-Musculoskeletal-Necropsy and histopathology of thigh muscle, sternebrae, vertebrae, femur (including bone marrow), costochondral junction (rib), and gross lesions-Gastrointestinal-Necropsy and histopathology of salivary gland, esophagus, stomach, gallbladder, duodenum, jejunum, ileum, colon, cecum, rectum, and gross lesions-Neurological/Behavioral-Necropsy and histopathology of sciatic nerve, brain, spinal cord, and gross lesions-Ocular/Sensory-Necropsy and histopathology of eyes and gross lesions-Lung/Respiratory-Necropsy and histopathology of nasal cavity, nasal turbinates, larynx, pharynx, trachea, lungs, bronchi, and gross lesions-Thyroid-Necropsy and histopathology of thyroid glands, parathyroids, and gross lesions-Other (please specify below) (Endocrine)-Necropsy and histopathology of pituitary gland, adrenal glands, pancreas, and gross lesions-Hepatic/Liver-Necropsy and histopathology of liver and gross lesions-Renal/Kidney-Necropsy and histopathology of kidneys, urinary bladder, and gross lesions-Cardiovascular-Necropsy and histopathology of heart and gross lesions-Other (please specify below) (Clinical signs)-Clinical signs, moribundity
Duration and Exposure Route:	Inhalation-Vapor-Duration: Short-term (>1-30 days)-5-6-2-week(s)-Inhalation-Vapor-Duration: Chronic (>90 days)-5-6-14-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	62372

Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	Medium	All critical information is reported. Some important information is not reported, including some animal husbandry conditions (including temperature and humidity) and parity of the animals; however, animals were only 4-5 weeks at the start of the study (~5 weeks for 2-week study; ~4-5 weeks for 14-week study). The test animal species, test article identity, concentrations tested and duration of exposure, route, quantitative or qualitative results for all endpoints examined, animal source, strain, age, sex, starting body weight, animal husbandry conditions (light/dark cycle), number of animals per cage, availability of food and water, test substance source, purity, method of administration, frequency of exposure, number of animals per group, and procedures used to measure endpoints were reported.
Domain 2: Selection and Performance			
	Metric 2: Allocation	High	The allocation method for assignment of animals to groups was based on random assignment (assignment based on a table of random numbers).
	Metric 3: Observational Bias / Blinding Changes	Medium	Measures to reduce observational bias were not reported and some of the endpoints were subjective (e.g., moribundity).
Domain 3: Confounding / Variable Control			

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Study Citation:	National Institutes of Health, Services, D.o. (1984). Toxicology and carcinogenesis studies of 1,3-butadiene (CAS no. 106-99-0) in B6C3F1 mice (inhalation studies). 288:1-111.
Health Outcome(s) and Reported Health Effect(s):	Mortality-Survival/mortality-Skin/Connective Tissue-Necropsy and histopathology of skin and gross lesions-Immune/Hematological-Necropsy and histopathology of mandibular lymph node, mesenteric lymph node, spleen, thymus, and gross lesions-Reproductive/Developmental-Necropsy and histopathology of mammary gland, seminal vesicles, prostate, testes, ovaries, uterus, and gross lesions-Musculoskeletal-Necropsy and histopathology of thigh muscle, sternebrae, vertebrae, femur (including bone marrow), costochondral junction (rib), and gross lesions-Gastrointestinal-Necropsy and histopathology of salivary gland, esophagus, stomach, gallbladder, duodenum, jejunum, ileum, colon, cecum, rectum, and gross lesions-Neurological/Behavioral-Necropsy and histopathology of sciatic nerve, brain, spinal cord, and gross lesions-Ocular/Sensory-Necropsy and histopathology of eyes and gross lesions-Lung/Respiratory-Necropsy and histopathology of nasal cavity, nasal turbinates, larynx, pharynx, trachea, lungs, bronchi, and gross lesions-Thyroid-Necropsy and histopathology of thyroid glands, parathyroids, and gross lesions-Other (please specify below) (Endocrine)-Necropsy and histopathology of pituitary gland, adrenal glands, pancreas, and gross lesions-Hepatic/Liver-Necropsy and histopathology of liver and gross lesions-Renal/Kidney-Necropsy and histopathology of kidneys, urinary bladder, and gross lesions-Cardiovascular-Necropsy and histopathology of heart and gross lesions-Other (please specify below) (Clinical signs)-Clinical signs, moribundity
Duration and Exposure Route:	Inhalation-Vapor-Duration: Short-term (>1-30 days)-5-6-2-week(s)-Inhalation-Vapor-Duration: Chronic (>90 days)-5-6-14-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	62372

Domain	Metric	Rating	Comments
Metric 4: Confounding / Variable Control	Low	There is some concern that confounding factors that may modify the results were uncontrolled due to incomplete reporting of animal husbandry (e.g., temperature, humidity, air changes). The study included an appropriate negative control. The control responses were appropriate for the outcomes reported. Animals were housed in stainless steel mesh cages. Contaminant levels in feed were measured; measurement of contaminants in bedding and water was not reported. Test substance purity was reported as 98.94 to 100%; small amounts of impurities were detected in the test substance, including methane and an unidentified substance.	
Domain 4: Selective Reporting and Attrition			
Metric 5: Selective Reporting and Attrition	High	All animals are accounted for in the presented results and there were no unexplained omissions or attrition. Quantitative or qualitative results were reported for all prespecified outcomes.	
Domain 5: Exposure Methods Sensitivity			
Metric 6: Chemical administration and characterization	Low	Some details of exposure administration were incompletely reported (e.g., whether whole-body or nose-only exposures). Purity was determined in a separate test. The test substance supplier was specified. Some details on timing (e.g., if animals were exposed at the same time of day to the extent possible) were incompletely reported. Additionally, test substance concentrations were not analytically determined.	
Metric 7: Exposure timing, frequency, and duration	High	The timing, duration, and frequency of the exposure appear to be appropriate for the study type and the outcomes/endpoints evaluated.	
Domain 6: Outcome Measures and Results Display			
Metric 8: Endpoint sensitivity and specificity	High	The procedures were sensitive and specific for the outcomes and endpoints of interest. The timing of the assessment of endpoints was appropriate.	

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Study Citation:	National Institutes of Health, Services, D.o. (1984). Toxicology and carcinogenesis studies of 1,3-butadiene (CAS no. 106-99-0) in B6C3F1 mice (inhalation studies). 288:1-111.
Health Outcome(s) and Reported Health Effect(s):	Mortality-Survival/mortality-Skin/Connective Tissue-Necropsy and histopathology of skin and gross lesions-Immune/Hematological-Necropsy and histopathology of mandibular lymph node, mesenteric lymph node, spleen, thymus, and gross lesions-Reproductive/Developmental-Necropsy and histopathology of mammary gland, seminal vesicles, prostate, testes, ovaries, uterus, and gross lesions-Musculoskeletal-Necropsy and histopathology of thigh muscle, sternebrae, vertebrae, femur (including bone marrow), costochondral junction (rib), and gross lesions-Gastrointestinal-Necropsy and histopathology of salivary gland, esophagus, stomach, gallbladder, duodenum, jejunum, ileum, colon, cecum, rectum, and gross lesions-Neurological/Behavioral-Necropsy and histopathology of sciatic nerve, brain, spinal cord, and gross lesions-Ocular/Sensory-Necropsy and histopathology of eyes and gross lesions-Lung/Respiratory-Necropsy and histopathology of nasal cavity, nasal turbinates, larynx, pharynx, trachea, lungs, bronchi, and gross lesions-Thyroid-Necropsy and histopathology of thyroid glands, parathyroids, and gross lesions-Other (please specify below) (Endocrine)-Necropsy and histopathology of pituitary gland, adrenal glands, pancreas, and gross lesions-Hepatic/Liver-Necropsy and histopathology of liver and gross lesions-Renal/Kidney-Necropsy and histopathology of kidneys, urinary bladder, and gross lesions-Cardiovascular-Necropsy and histopathology of heart and gross lesions-Other (please specify below) (Clinical signs)-Clinical signs, moribundity
Duration and Exposure Route:	Inhalation-Vapor-Duration: Short-term (>1-30 days)-5-6-2-week(s)-Inhalation-Vapor-Duration: Chronic (>90 days)-5-6-14-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	62372

Domain	Metric	Rating	Comments
	Metric 9: Results presentation	Uninformative	Some details of the results presentation were missing (e.g., individual animal data). Mean values are provided with variance (+/-SEM) for body weight data. Necropsy results are reported qualitatively (no compound-related effects). However, individual data were not presented for body weights. According to the NTP report (HERO ID 62372, p. 10), the 14-week studies were performed from May to Sept 1977 by Industrial Bio-test Laboratories. According to Table 1, the 2-week study was conducted by the same laboratory. It is presumed this was performed during the same timeframe. EPA considers the reporting of data in studies conducted by Industrial Bio-Test (IBT) laboratories during 1960-1978 to be unacceptable due to concerns about the integrity of the lab (i.e., discrepancies between raw data and study report, and gross deficiencies in study conduct were identified during an inspection by the FDA in 1976 and a follow-up audit by EPA and in collaboration with the Canadian Health and Welfare Department). Therefore, this metric and the data from these assays is uninformative.

Overall Quality Determination**Uninformative**

Study Citation:	Pacchierotti, F., Tiveron, C., Ranaldi, R., Bassani, B., Cordelli, E., Leter, G., Spano, M. (1998). Reproductive toxicity of 1,3-butadiene in the mouse: Cytogenetic analysis of chromosome aberrations in first-cleavage embryos and flow cytometric evaluation of spermatogonial cell killing. <i>Mutation Research</i> 397(1):55-66.
Health Outcome(s) and Reported	Reproductive/Developmental-Male reproductive capacity (percentages of mated females and unfertilized metaphase II oocytes); testis weights; detailed analysis of testicular cells (counts of early and mature spermatids, G1 and G2 spermatogonia, primary and secondary spermatocytes, testicular somatic cells, and tetraploid cells as well as evaluation of cytotoxicity).
Health Effect(s):	
Duration and	
Exposure Route:	Inhalation-Gas-Duration: Short-term (>1-30 days)-F0- pre mating (5 days)
Species:	Mouse-Other ((102/E1 x C3H/E1)F1)-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	5553772

Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
Metric 1:	Reporting Quality	Low	All critical and most important information was reported. Male (102/E1 x C3H/E1)F1 mice (age, number of animals, and source were reported) were exposed via whole body inhalation to 1,3-butadiene (CASRN provided) gas concentrations of 0, 130, 500 1300 ppm, for 6 hrs/day, for 5 consecutive days. Most endpoint evaluation methods were described and quantitative results were reported for at least one endpoint of interest. The missing information included the test substance purity and source, initial body weights, parity of untreated females, most animal husbandry details (only food availability was noted), and the number of animals per cage. The significant amount of missing details is expected to reduce the ability to evaluate the study.
Domain 2: Selection and Performance			
Metric 2:	Allocation	Low	The study did not report how animals were allocated into study groups, or if animals were normalized to body weight.
Metric 3:	Observational Bias / Blinding Changes	Medium	No blinding was mentioned in the study; however, no endpoints were subjective in nature or were measured using automated systems (e.g., flow cytometry).
Domain 3: Confounding / Variable Control			

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Study Citation:	Pacchierotti, F., Tiveron, C., Ranaldi, R., Bassani, B., Cordelli, E., Leter, G., Spano, M. (1998). Reproductive toxicity of 1,3-butadiene in the mouse: Cytogenetic analysis of chromosome aberrations in first-cleavage embryos and flow cytometric evaluation of spermatogonial cell killing. <i>Mutation Research</i> 397(1):55-66.
Health Outcome(s) and Reported	Reproductive/Developmental-Male reproductive capacity (percentages of mated females and unfertilized metaphase II oocytes); testis weights; detailed analysis of testicular cells (counts of early and mature spermatids, G1 and G2 spermatogonia, primary and secondary spermatocytes, testicular somatic cells, and tetraploid cells as well as evaluation of cytotoxicity).
Health Effect(s):	
Duration and Exposure Route:	Inhalation-Gas-Duration: Short-term (>1-30 days)-F0- pre mating (5 days)
Species:	Mouse-Other ((102/E1 x C3H/E1)F1)-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	5553772

Domain	Metric	Rating	Comments
Metric 4: Confounding / Variable Control	Low	This study conducted exposures two years apart (low and high concentrations during first experiment, and a mid concentration during the second experiment). Each experiment contained its own negative (sham air only) controls. Exposure conditions were the same. No animal husbandry details were provided, and the study did not report initial animal body weights, which makes it difficult to determine any possible confounding. Reflex bradypnea was not assessed; however, test chemical is an irritant in humans but not in animals. This was a non-guideline study and it is not clear that positive controls were warranted. Since each exposure experiment included its own control, the 2-year difference in exposure times is not considered to be a critical defect (the data can be evaluated as separate independent experiments); however, the authors combined the data in several instances (e.g., for evaluation of dose-related trends), which may not have been appropriate (this issue is addressed separately in metric 6.1). Prior to mating, females were administered hormones to promote ovulation. The authors noted that the exogenous hormone treatment in the second exposure experiment may not have been overly effective; the authors may have wrongly diagnosed vaginal-plugs. It was not indicated if this was the case for both exposed and control animals.	
Domain 4: Selective Reporting and Attrition			
Metric 5: Selective Reporting and Attrition	Medium	No deaths were inferred from the information in the text (all males were mated). There is no evidence of selective reporting; results from all groups are reported for each endpoint, although sample sizes are often described in the text, but are not reported in the data tables.	
Domain 5: Exposure Methods Sensitivity			
Metric 6: Chemical administration and characterization	Medium	Some information regarding chemical administration and characterization are missing. The test substance CASRN was reported, but the source and purity were not specified, and the performing laboratory did not analytically verify the test substance. Limited to no details on atmosphere generation or exposure conditions were provided in the current study, but Adler et al. (1994; hero ID 2448931) was cited for methodological details. This citation was reviewed for this evaluation and methods were generally adequately described (air changes per hour was not specified). Animals were exposed whole body, the number of animals per cage during exposure was not specified. The study noted that test concentrations were monitored by gas chromatography, but no analytical measurements were reported, and it was not specified whether measured values were close to the target.	

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Study Citation:	Pacchierotti, F., Tiveron, C., Ranaldi, R., Bassani, B., Cordelli, E., Leter, G., Spano, M. (1998). Reproductive toxicity of 1,3-butadiene in the mouse: Cytogenetic analysis of chromosome aberrations in first-cleavage embryos and flow cytometric evaluation of spermatogonial cell killing. <i>Mutation Research</i> 397(1):55-66.
Health Outcome(s) and Reported	Reproductive/Developmental-Male reproductive capacity (percentages of mated females and unfertilized metaphase II oocytes); testis weights; detailed analysis of testicular cells (counts of early and mature spermatids, G1 and G2 spermatogonia, primary and secondary spermatocytes, testicular somatic cells, and tetraploid cells as well as evaluation of cytotoxicity).
Health Effect(s):	
Duration and Exposure Route:	Inhalation-Gas-Duration: Short-term (>1-30 days)-F0- pre mating (5 days)
Species:	Mouse-Other ((102/E1 x C3H/E1)F1)-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	5553772

Domain	Metric	Rating	Comments
Metric 7:	Exposure timing, frequency, and duration	High	Animals were exposed for 6hrs/day for 5 consecutive days. No specific justification was provided, but the frequency and duration were consistent with a cited study performed by a different group and seemed appropriate for the purposes of the study.

Domain 6: Outcome Measures and Results Display

Metric 8:	Endpoint sensitivity and specificity	Low	The outcome assessment methodology was clearly described and appropriate for the outcomes of interest. The study used (102/E1 x C3H/E1)F1 male mice. No specific justification was provided and it was noted that the spermatozoa of this strain were resistant to DEB toxicity (a 1,3-butadiene metabolic intermediate). In other studies, B6C3F1 mice were used. It is unclear if the strain used was the most appropriate. The number of animals was acceptable. The sample sizes were reported in the text, but not in the data tables; the sample sizes were sufficient for conducting statistical analysis. When the two exposure experiments are combined, the number of groups (3 plus controls) was appropriate. It is likely that the concentration spacing in the first experiment was too broad, prompting the addition of a mid-concentration group at a later time.
Metric 9:	Results presentation	Low	Data for all groups were reported as means \pm SD where appropriate and the methods of statistical analyses were clearly described. In some cases, it appears that the control data from the two exposures (conducted 2 years apart) were pooled (see Table 1), which was likely not appropriate. In another instance, data from both experiments were plotted together and analyzed for a dose-response (see Fig. 3).

Overall Quality Determination

Low

Study Citation:	Pacchierotti, F., Tiveron, C., Ranaldi, R., Bassani, B., Cordelli, E., Leter, G., Spano, M. (1998). Reproductive toxicity of 1,3-butadiene in the mouse: Cytogenetic analysis of chromosome aberrations in first-cleavage embryos and flow cytometric evaluation of spermatogonial cell killing. <i>Mutation Research</i> 397(1):55-66.
Health Outcome(s) and Reported	Other (please specify below) (Genotoxicity)-Chromosome aberrations in zygotes; sperm chromatin structure assay (SCSA)
Health Effect(s):	
Duration and Exposure Route:	Inhalation-Gas-Duration: Short-term (>1-30 days)-F0- pre mating (5 days)
Species:	Mouse-Other ((102/E1 x C3H/E1)F1)-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	5553772

Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	Low	All critical and most important information was reported. Male (102/E1 x C3H/E1)F1 mice (age, number of animals, and source were reported) were exposed via whole body inhalation to 1,3-butadiene (CASRN provided) gas concentrations of 0, 130, 500 1300 ppm, for 6 hrs/day, for 5 consecutive days. Most endpoint evaluation methods were described and quantitative results were reported for at least one endpoint of interest. The missing information included the test substance purity and source, initial body weights, parity of untreated females, most animal husbandry details (only food availability was noted), and the number of animals per cage. The significant amount of missing details is expected to reduce the ability to evaluate the study.
Domain 2: Selection and Performance			
	Metric 2: Allocation	Low	The study did not report how animals were allocated into study groups, or if animals were normalized to body weight.
	Metric 3: Observational Bias / Blinding Changes	Medium	No blinding was mentioned in the study; however, no endpoints were subjective in nature or were measured using automated systems (e.g., flow cytometry).
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	Low	This study conducted exposures two years apart (low and high concentrations during the first experiment, and a mid concentration during the second experiment. Each contained its own negative (sham air only) controls. Exposure conditions were the same. No animal husbandry details were provided, and the study did not report initial animal body weights, which makes it difficult to determine any possible confounding. Reflex bradypnea was not assessed in an inhalation study. The test chemical is an irritant in humans, but not in animals. This was a non-guideline study and it is not clear that positive controls were warranted. Since each exposure experiment included its own control, the 2-year difference in exposure times is not considered to be a critical defect (the data can be evaluated as separate independent experiments); however, the authors appear to pool control data which could have a significant influence on the ability to interpret the study results. Prior to mating, females were administered hormones to promote ovulation. The authors noted that the exogenous hormone treatment in the second exposure experiment may not have been overly effective. The authors may have wrongly diagnosed vaginal plugs.
Domain 4: Selective Reporting and Attrition			

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Study Citation:	Pacchierotti, F., Tiveron, C., Ranaldi, R., Bassani, B., Cordelli, E., Leter, G., Spano, M. (1998). Reproductive toxicity of 1,3-butadiene in the mouse: Cytogenetic analysis of chromosome aberrations in first-cleavage embryos and flow cytometric evaluation of spermatogonial cell killing. <i>Mutation Research</i> 397(1):55-66.
Health Outcome(s) and Reported	Other (please specify below) (Genotoxicity)-Chromosome aberrations in zygotes; sperm chromatin structure assay (SCSA)
Health Effect(s):	
Duration and Exposure Route:	Inhalation-Gas-Duration: Short-term (>1-30 days)-F0- pre mating (5 days)
Species:	Mouse-Other ((102/E1 x C3H/E1)F1)-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	5553772

Domain	Metric	Rating	Comments
Metric 5:	Selective Reporting and Attrition	Medium	No deaths were inferred from the information in the text (all males were mated). There is no evidence of selective reporting; results from all groups are reported for each endpoint, although sample sizes are often described in the text, but are not reported in the data tables.

Domain 5: Exposure Methods Sensitivity

Metric 6:	Chemical administration and characterization	Medium	Some information regarding chemical administration and characterization are missing. The test substance CASRN was reported, but the source and purity were not specified, and the performing laboratory did not analytically verify the test substance. Limited to no details on atmosphere generation or exposure conditions were provided in the current study, but Adler et al. (1994; hero ID 2448931) was cited for methodological details. This citation was reviewed for this evaluation and methods were generally adequately described (air changes per hour was not specified). Animals were exposed whole body, the number of animals per cage during exposure was not specified. The study noted that test concentrations were monitored by gas chromatography, but no analytical measurements were reported, and it was not specified whether measured values were close to the target.
Metric 7:	Exposure timing, frequency, and duration	High	Animals were exposed for 6hrs/day for 5 consecutive days. No specific justification was provided, but the frequency and duration were consistent with a cited study performed by a different group and seemed appropriate for the purposes of the study.

Domain 6: Outcome Measures and Results Display

Metric 8:	Endpoint sensitivity and specificity	Low	The outcome assessment methodology was clearly described and appropriate for the outcomes of interest. However, the authors noted that the sperm chromatin structure assay (SCSA) is sensitive, but that there are unknowns regarding what influences the susceptibility of sperm chromatin to the acidic denaturation step. The study used (102/E1 x C3H/E1)F1 male mice. No specific justification was provided and it was noted that the spermatozoa of this strain were resistant to DEB toxicity (a 1,3-butadiene metabolic intermediate). In other studies, B6C3F1 mice were used. It is unclear if the strain used was the most appropriate. The number of animals was acceptable. The sample sizes were reported in the text for the SCSA assay and in the data table for cytogenetic analysis in zygotes. The numbers were sufficient for conducting statistical analysis. When the two exposure experiments are combined, the number of groups (3 plus controls) was appropriate. It is likely that the concentration spacing in the first experiment was too broad, prompting the addition of a mid-concentration group at a later time.
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Study Citation:	Pacchierotti, F., Tiveron, C., Ranaldi, R., Bassani, B., Cordelli, E., Leter, G., Spano, M. (1998). Reproductive toxicity of 1,3-butadiene in the mouse: Cytogenetic analysis of chromosome aberrations in first-cleavage embryos and flow cytometric evaluation of spermatogonial cell killing. <i>Mutation Research</i> 397(1):55-66.
Health Outcome(s) and Reported	Other (please specify below) (Genotoxicity)-Chromosome aberrations in zygotes; sperm chromatin structure assay (SCSA)
Health Effect(s):	
Duration and Exposure Route:	Inhalation-Gas-Duration: Short-term (>1-30 days)-F0- premating (5 days)
Species:	Mouse-Other ((102/E1 x C3H/E1)F1)-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	5553772

Domain	Metric	Rating	Comments
	Metric 9: Results presentation	Low	Data for all groups were reported as means \pm SD where appropriate and the methods of statistical analysis were clearly described. In some cases, it appears that the control data from the two exposures (conducted 2 years apart) were pooled (see Tables 3 and 4), which was likely not appropriate and significantly impacts the ability to interpret the study results.

Overall Quality Determination**Low**

Study Citation:	Anderson, D., Edwards, A. J., Brinkworth, M. H., Hughes, J. A. (1996). Male-mediated F1 effects in mice exposed to 1,3-butadiene. <i>Toxicology</i> 113(1-3):120-127.
Health Outcome(s) and Reported	Reproductive/Developmental-Fetal skeletal abnormalities, % mated, % females pregnant, number of implantations, early and late deaths, late deaths including dead fetuses, number of abnormal fetuses.-Other (please specify below) (Genotoxicity)-Dominant lethality
Health Effect(s):	
Duration and Exposure Route:	Inhalation-Gas-Duration: Subchronic (>30-90 days)-1-F0- pre mating (10 weeks)
Species:	Mouse-CD-1 - [mouse]-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	5663561

Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	Low	All critical and some important information was reported. The test material was identified as 1,3-butadiene in the title and abstract. A source was specified. CD-1 mice (sex and source reported) were acutely exposed, whole body, to 0, 12.5, or 1,250 ppm 6 hrs/day, 5 days/week for 10 weeks. The number of animals per group was reported. Missing information included the test substance purity, animal age, starting body weights, parity of unexposed females, and all animal husbandry details. A citation was provided for standard practices (an IARC book publication). Endpoint evaluation methods and qualitative or quantitative results for at least one endpoint were reported. The missing information is expected to reduce the ability to evaluate the study.
Domain 2: Selection and Performance			
	Metric 2: Allocation	Low	The study did not report how animals were allocated into study groups, or if animals were normalized to body weight.
	Metric 3: Observational Bias / Blinding Changes	Medium	No blinding was mentioned in the study; however, no endpoints were subjective or blinding is not required according to current guidelines.
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	Low	Negative controls were exposed to ambient air only. Limited to no quantitative data were provided, so it is unclear whether the negative control responses were appropriate. The study monitored dimer concentrations in the exposure atmosphere and reported a range from 3 to 133 ppm (results per group were not specified). It is unclear what impact the presence of the dimer may have had on the study results. A dimer concentration of 225 ppm was noted in one instance (group not specified). Although positive controls are generally not required for reproductive/developmental studies, this was a dominant lethality study, and positive controls are generally required (OECD TG 478). The authors did not indicate previous experience with this type of assay. Other details to determine confounding (e.g., animal body weights, and husbandry conditions) were not reported. Additionally, reflex bradypnea was not assessed; however, the chemical is a respiratory irritant in humans but not in animals.
Domain 4: Selective Reporting and Attrition			

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Study Citation:	Anderson, D., Edwards, A. J., Brinkworth, M. H., Hughes, J. A. (1996). Male-mediated F1 effects in mice exposed to 1,3-butadiene. <i>Toxicology</i> 113(1-3):120-127.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Fetal skeletal abnormalities, % mated, % females pregnant, number of implantations, early and late deaths, late deaths including dead fetuses, number of abnormal fetuses.-Other (please specify below) (Genotoxicity)-Dominant lethality
Duration and Exposure Route:	Inhalation-Gas-Duration: Subchronic (>30-90 days)-1-F0- premating (10 weeks)
Species:	Mouse-CD-1 - [mouse]-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	5663561

Domain	Metric	Rating	Comments
Metric 5:	Selective Reporting and Attrition	High	Two males in the high-exposure group died. Given the number of animals used in the study, these deaths are not expected to have a significant impact on the other endpoints evaluated. Data are reported quantitatively or qualitatively for all of the endpoints.

Domain 5: Exposure Methods Sensitivity

Metric 6:	Chemical administration and characterization	Low	Limited details on the test substance were provided. The source (ICI plc) no longer exists, and the test substance purity was not provided. The performing laboratory did not independently verify the test substance. The test atmospheres were monitored for the presence of the dimer, but no data reporting analytical measurements of the test substance were provided. It is unclear whether the reported concentrations were target or nominal. The chambers were described as being closed and animals were exposed whole body. It was not explicitly stated whether the chambers were static or dynamic. The number of animals per cage was not specified. Storage of the test substance was reported and was appropriate.
Metric 7:	Exposure timing, frequency, and duration	High	For the purposes of determining whether a chemical induces dominant lethality, a repeated exposure of 6hrs/day, 5 days/week for 10 weeks followed by a single mating is generally consistent with OECD TG 478.

Domain 6: Outcome Measures and Results Display

Metric 8:	Endpoint sensitivity and specificity	Medium	This study conducted a modified dominant lethality assay. The authors describe the study design as one that "straddles the fields of genetic, reproductive, and developmental toxicity". Females were killed on GD17, rather than between GDs 12-15, allowing assessment of an additional classification of post-implantation deaths (i.e., dead fetuses: those that died immediately prior to examination). The outcome methods were generally consistent with those assessed in a standard dominant lethality study (OECD 428); however, the methods were described with limited details. The animal species/strain and number of animals per group were adequate. The age and parity of females were not reported. Sampling was not clearly defined for some endpoints. For example, skeletal malformations were assessed on (grossly) malformed fetuses and "randomly selected normal litter mates and controls;" the number of animals randomly selected is not clearly reported and is inconsistent across groups (Table 4). The concentrations and concentration spacing were not explicitly justified but were consistent with concentrations used in other similar studies. However, only two exposure groups were used instead of the recommended 3.
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Study Citation:	Anderson, D., Edwards, A. J., Brinkworth, M. H., Hughes, J. A. (1996). Male-mediated F1 effects in mice exposed to 1,3-butadiene. <i>Toxicology</i> 113(1-3):120-127.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Fetal skeletal abnormalities, % mated, % females pregnant, number of implantations, early and late deaths, late deaths including dead fetuses, number of abnormal fetuses.-Other (please specify below) (Genotoxicity)-Dominant lethality
Duration and Exposure Route:	Inhalation-Gas-Duration: Subchronic (>30-90 days)-1-F0- premating (10 weeks)
Species:	Mouse-CD-1 - [mouse]-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	5663561

Domain	Metric	Rating	Comments
Metric 9:	Results presentation	Medium	Quantitative results were provided for most endpoints and groups and were presented as means \pm SD where appropriate. The methods used for statistical analysis were reported in footnotes. It is unclear whether the males were used as the statistical unit for dominant lethality measures.

Overall Quality Determination**Medium**

Study Citation: Anderson, D., Edwards, A. J., Brinkworth, M. H., Hughes, J. A. (1996). Male-mediated F1 effects in mice exposed to 1,3-butadiene. *Toxicology* 113(1-3):120-127.

Health Outcome(s) and Reported Health Effect(s): Nutritional/Metabolic-Body weights

Duration and Exposure Route: Inhalation-Gas-Duration: Subchronic (>30-90 days)-1-F0- pre mating (10 weeks)

Species: Mouse-CD-1 - [mouse]-Male

Chemical: 1,3-Butadiene- Parent compound

HERO ID: 5663561

Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	Low	All critical and some important information was reported. The test material was identified as 1,3-butadiene in the title and abstract. A source was specified. CD-1 mice (sex and source reported) were acutely exposed, whole body, to 0, 12.5, or 1,250 ppm 6 hrs/day, 5 days/week for 10 weeks. The number of animals per group was reported. Missing information included the test substance purity, animal age, starting body weights, parity of unexposed females, and all animal husbandry details. A citation was provided for standard practices (an IARC book publication). Endpoint evaluation methods and qualitative or quantitative results for at least one endpoint were reported. The missing information is expected to reduce the ability to evaluate the study.
Domain 2: Selection and Performance			
	Metric 2: Allocation	Low	The study did not report how animals were allocated into study groups, or if animals were normalized to body weight.
	Metric 3: Observational Bias / Blinding Changes	Medium	No blinding was mentioned in the study; however, no endpoints were subjective or blinding is not required according to current guidelines.
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	Low	Negative controls were exposed to ambient air only. Limited to no quantitative data were provided, so it is unclear whether the negative control responses were appropriate. The study monitored dimer concentrations in the exposure atmosphere and reported a range from 3 to 133 ppm (results per group were not specified). It is unclear what impact the presence of the dimer may have had on the study results. A dimer concentration of 225 ppm was noted in one instance (group not specified). Although positive controls are generally not required for reproductive/developmental studies, this was a dominant lethality study, and positive controls are generally required (OECD TG 478). The authors did not indicate previous experience with this type of assay. Other details to determine confounding (e.g., animal body weights, and husbandry conditions) were not reported. Additionally, reflex bradypnea was not assessed; however, the chemical is a respiratory irritant in humans but not in animals.
Domain 4: Selective Reporting and Attrition			
	Metric 5: Selective Reporting and Attrition	High	Two males in the high-exposure group died. Given the number of animals used in the study, these deaths are not expected to have a significant impact on the other endpoints evaluated. Data are reported quantitatively or qualitatively for all of the endpoints.

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Study Citation: Anderson, D., Edwards, A. J., Brinkworth, M. H., Hughes, J. A. (1996). Male-mediated F1 effects in mice exposed to 1,3-butadiene. *Toxicology* 113(1-3):120-127.

Health Outcome(s) and Reported Health Effect(s): Nutritional/Metabolic-Body weights

Duration and Exposure Route: Inhalation-Gas-Duration: Subchronic (>30-90 days)-1-F0- pre mating (10 weeks)

Species: Mouse-CD-1 - [mouse]-Male

Chemical: 1,3-Butadiene- Parent compound

HERO ID: 5663561

Domain	Metric	Rating	Comments
Domain 5: Exposure Methods Sensitivity			
	Metric 6: Chemical administration and characterization	Low	Limited details on the test substance were provided. The source (ICI plc) no longer exists, and the test substance purity was not provided. The performing laboratory did not independently verify the test substance. The test atmospheres were monitored for the presence of the dimer, but no data reporting analytical measurements of the test substance were provided. It is unclear whether the reported concentrations were target or nominal. The chambers were described as being closed and animals were exposed whole body. It was not explicitly stated whether the chambers were static or dynamic. The number of animals per cage was not specified. Storage of the test substance was reported and was appropriate.
	Metric 7: Exposure timing, frequency, and duration	High	For the purposes of determining whether a chemical induces dominant lethality, a repeated exposure of 6hrs/day, 5 days/week for 10 weeks followed by a single mating is generally consistent with OECD TG 478.
Domain 6: Outcome Measures and Results Display			
	Metric 8: Endpoint sensitivity and specificity	Low	This study conducted a modified dominant lethality assay. The authors describe the study design as one that "straddles the fields of genetic, reproductive, and developmental toxicity". The outcome methods were generally consistent with those assessed in a standard dominant lethality study (OECD 428); however, the methods were described with limited details. No mention of body weight measurements was mentioned in the methods; however, the results indicated that "no treatment-related effects were seen on the body weights of surviving animals (data not shown)." It is unclear which group of animals these results are referring to (exposed males, pregnant females?) or when, and at what frequency body weights were measured. The animal species/strain and number of animals per group were adequate. The age and parity of females were not reported. Sampling was not clearly defined for some endpoints. The concentrations and concentration spacing were not explicitly justified but were consistent with concentrations used in other similar studies. However, only two exposure groups were used instead of the recommended 3.
	Metric 9: Results presentation	Uninformative	A qualitative statement of "no treatment-related effects were seen on the body weights of surviving animals (data not shown)" was provided. It is unclear which group of animals these results are referring to (exposed males, pregnant females?). In the absence of methodological information on the outcome assessment in combination with poor data reporting, the results, as described, cannot be interpreted.

Overall Quality Determination

Uninformative

Study Citation:	Anderson, D., Edwards, A. J., Brinkworth, M. H., Hughes, J. A. (1996). Male-mediated F1 effects in mice exposed to 1,3-butadiene. <i>Toxicology</i> 113(1-3):120-127.		
Health Outcome(s) and Reported Health Effect(s):	Cancer/Carcinogenesis-Tumor incidence in F1 offspring		
Duration and Exposure Route:	Inhalation-Gas-Duration: Subchronic (>30-90 days)-1-F0- pre mating (10 weeks)		
Species:	Mouse-CD-1 - [mouse]-Male		
Chemical:	1,3-Butadiene- Parent compound		
HERO ID:	5663561		
Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	Low	All critical and some important information was reported. The test material was identified as 1,3-butadiene in the title and abstract. A source was specified. CD-1 mice (sex and source reported) were acutely exposed, whole body, to 0, 12.5, or 1,250 ppm 6 hrs/day, 5 days/week for 10 weeks. The number of animals per group was reported. Missing information included the test substance purity, animal age, starting body weights, parity of unexposed females, and all animal husbandry details. A citation was provided for standard practices (an IARC book publication). Endpoint evaluation methods and qualitative or quantitative results for at least one endpoint were reported. The missing information is expected to reduce the ability to evaluate the study.
Domain 2: Selection and Performance			
	Metric 2: Allocation	Low	The study did not report how animals were allocated into study groups, or if animals were normalized to body weight.
	Metric 3: Observational Bias / Blinding Changes	Medium	No blinding was mentioned in the study; however, no endpoints were subjective or blinding is not required according to current guidelines.
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	Low	Negative controls were exposed to ambient air only. Limited to no quantitative data were provided, so it is unclear whether the negative control responses were appropriate. The study monitored dimer concentrations in the exposure atmosphere and reported a range from 3 to 133 ppm (results per group were not specified). It is unclear what impact the presence of the dimer may have had on the study results. A dimer concentration of 225 ppm was noted in one instance (group not specified). Although positive controls are generally not required for reproductive/developmental studies, this was a dominant lethality study, and positive controls are generally required (OECD TG 478). The authors did not indicate previous experience with this type of assay. Other details to determine confounding (e.g., animal body weights, and husbandry conditions) were not reported. Additionally, reflex bradypnea was not assessed; however, the chemical is a respiratory irritant in humans but not in animals.
Domain 4: Selective Reporting and Attrition			
	Metric 5: Selective Reporting and Attrition	High	Two males in the high-exposure group died. Given the number of animals used in the study, these deaths are not expected to have a significant impact on the other endpoints evaluated. Data are reported quantitatively or qualitatively for all of the endpoints.

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Study Citation: Anderson, D., Edwards, A. J., Brinkworth, M. H., Hughes, J. A. (1996). Male-mediated F1 effects in mice exposed to 1,3-butadiene. *Toxicology* 113(1-3):120-127.

Health Outcome(s) and Reported Health Effect(s): Cancer/Carcinogenesis-Tumor incidence in F1 offspring

Duration and Exposure Route: Inhalation-Gas-Duration: Subchronic (>30-90 days)-1-F0- pre mating (10 weeks)

Species: Mouse-CD-1 - [mouse]-Male

Chemical: 1,3-Butadiene- Parent compound

HERO ID: 5663561

Domain	Metric	Rating	Comments
Domain 5: Exposure Methods Sensitivity			
	Metric 6: Chemical administration and characterization	Low	Limited details on the test substance were provided. The source (ICI plc) no longer exists, and the test substance purity was not provided. The performing laboratory did not independently verify the test substance. The test atmospheres were monitored for the presence of the dimer, but no data reporting analytical measurements of the test substance were provided. It is unclear whether the reported concentrations were target or nominal. The chambers were described as being closed and animals were exposed whole body. It was not explicitly stated whether the chambers were static or dynamic. The number of animals per cage was not specified. Storage of the test substance was reported and was appropriate.
	Metric 7: Exposure timing, frequency, and duration	Uninformative	The exposure timing, frequency, and duration are not appropriate for assessing carcinogenicity.
Domain 6: Outcome Measures and Results Display			
	Metric 8: Endpoint sensitivity and specificity	Low	This study conducted a modified dominant lethality assay. The authors describe the study design as one that "straddles the fields of genetic, reproductive, and developmental toxicity". F1 offspring were examined grossly for tumors after 75 weeks. It does not appear that the tumors were histologically examined. No further details were provided. The concentrations and concentration spacing were not explicitly justified but were consistent with concentrations used in other similar studies. However, only two exposure groups were used instead of the recommended 3.
	Metric 9: Results presentation	Uninformative	Quantitative results were provided. The numbers of animals with tumors (and time of observation) were provided, but not as incidences. The total number of animals examined was not reported making it difficult to adequately interpret the study results.

Overall Quality Determination

Uninformative

Study Citation:	Anderson, D., Edwards, A. J., Brinkworth, M. H., Hughes, J. A. (1996). Male-mediated F1 effects in mice exposed to 1,3-butadiene. <i>Toxicology</i> 113(1-3):120-127.		
Health Outcome(s) and Reported Health Effect(s):	Other (please specify below) (Genotoxicity)-Karyotyping in F1 fetal livers		
Duration and Exposure Route:	Inhalation-Gas-Duration: Subchronic (>30-90 days)-1-F0- pre mating (10 weeks)		
Species:	Mouse-CD-1 - [mouse]-Male		
Chemical:	1,3-Butadiene- Parent compound		
HERO ID:	5663561		
Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	Low	All critical and some important information was reported. The test material was identified as 1,3-butadiene in the title and abstract. A source was specified. CD-1 mice (sex and source reported) were acutely exposed, whole body, to 0, 12.5, or 1,250 ppm 6 hrs/day, 5 days/week for 10 weeks. The number of animals per group was reported. Missing information included the test substance purity, animal age, starting body weights, parity of unexposed females, and all animal husbandry details. A citation was provided for standard practices (an IARC book publication). Endpoint evaluation methods and qualitative or quantitative results for at least one endpoint were reported. The missing information is expected to reduce the ability to evaluate the study.
Domain 2: Selection and Performance			
	Metric 2: Allocation	Low	The study did not report how animals were allocated into study groups, or if animals were normalized to body weight.
	Metric 3: Observational Bias / Blinding Changes	Medium	No blinding was mentioned in the study; however, no endpoints were subjective or blinding is not required according to current guidelines.
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	Low	Negative controls were exposed to ambient air only. No quantitative data were provided, so it is unclear whether the negative control responses were appropriate. The study monitored dimer concentrations in the exposure atmosphere and reported a range from 3 to 133 ppm (results per group were not specified). It is unclear what impact the presence of the dimer may have had on the study results. Although positive controls are generally not required for reproductive/developmental studies, positive controls may have been appropriate for karyotyping. Other details to determine confounding (e.g., animal body weights, and husbandry conditions) were not reported. Additionally, reflex bradypnea was not assessed; however, the chemical is a respiratory irritant in humans but not in animals.
Domain 4: Selective Reporting and Attrition			
	Metric 5: Selective Reporting and Attrition	High	Two males in the high-exposure group died. Given the number of animals used in the study, these deaths are not expected to have a significant impact on the other endpoints evaluated. Data are reported quantitatively or qualitatively for all of the endpoints.
Domain 5: Exposure Methods Sensitivity			

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Study Citation: Anderson, D., Edwards, A. J., Brinkworth, M. H., Hughes, J. A. (1996). Male-mediated F1 effects in mice exposed to 1,3-butadiene. *Toxicology* 113(1-3):120-127.

Health Outcome(s) and Reported Health Effect(s): Other (please specify below) (Genotoxicity)-Karyotyping in F1 fetal livers

Duration and Exposure Route: Inhalation-Gas-Duration: Subchronic (>30-90 days)-1-F0- pre mating (10 weeks)

Species: Mouse-CD-1 - [mouse]-Male

Chemical: 1,3-Butadiene- Parent compound

HERO ID: 5663561

Domain	Metric	Rating	Comments
	Metric 6: Chemical administration and characterization	Low	Limited details on the test substance were provided. The source (ICI plc) no longer exists, and the test substance purity was not provided. The performing laboratory did not independently verify the test substance. The test atmospheres were monitored for the presence of the dimer, but no data reporting analytical measurements of the test substance were provided. It is unclear whether the reported concentrations were target or nominal. The chambers were described as being closed and animals were exposed whole body. It was not explicitly stated whether the chambers were static or dynamic. The number of animals per cage was not specified. Storage of the test substance was reported and was appropriate.
	Metric 7: Exposure timing, frequency, and duration	Low	It is unclear whether the study exposure frequency, timing, and duration were appropriate for this outcome of interest.
Domain 6: Outcome Measures and Results Display			
	Metric 8: Endpoint sensitivity and specificity	Uninformative	No methodological details of the outcome assessment methods were provided including the number of fetuses examined. It is unclear if the methods used were consistent with standard practices for evaluating chromosome aberrations. The concentrations and concentration spacing were not explicitly justified. Only two groups were included. The animal species/strain and number of animals per group were adequate. The age and parity of females were not reported.
	Metric 9: Results presentation	Low	Only a qualitative statement indicating that all karyotypes were normal was provided.

Overall Quality Determination

Uninformative

Study Citation:	Bevan, C., Stadler, J. C., Elliott, G. S., Frame, S. R., Baldwin, J. K., Leung, H. W., Moran, E., Panepinto, A. S. (1996). Subchronic toxicity of 4-vinylcyclohexene in rats and mice by inhalation exposure. <i>Fundamental and Applied Toxicology</i> 32(1):1-10.
Health Outcome(s) and Reported Health Effect(s):	Mortality-Mortality and moribundity-Nutritional/Metabolic-Weekly body weights; food consumption-Immune/Hematological-Hematology, spleen weight, gross necropsy, histopathology (bone marrow (sternal and femoral), mesenteric and mandibular lymph nodes, spleen, thymus)-Hepatic/Liver-Clinical chemistry (ALP, ALT, ASP, total protein, albumin, globulin, cholesterol, glucose, total bilirubin), liver weights, gross necropsy, histopathology-Renal/Kidney-Serum chemistry (BUN, creatinine, electrolytes), urinalysis, organ weight, gross necropsy, histopathology-Cardiovascular-Heart weight, gross necropsy, histopathology (aorta, heart)-Other (please specify below) (Endocrine)-Adrenal weights (rats only), gross necropsy, histopathology (pancreas, pituitary, adrenal glands)-Reproductive/Developmental-Organ weights: Testes, ovary (rats only); gross necropsy, histopathology (prostate, testes, epididymides, seminal vesicles, mammary gland, ovaries, uterus,vagina)-Neurological/Behavioral-Brain weight, gross pathology, histopathology (brain, spinal cord, sciatic nerve)-Gastrointestinal-Gross necropsy; histopathology (salivary glands, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, rectum gall-bladder (mice only))-Thyroid-Gross pathology; histopathology (thyroid, parathyroid)-Lung/Respiratory-Gross necropsy, histopathology (trachea, lungs, nose, larynx, pharynx)-Ocular/Sensory-Gross pathology; histopathology (eyes (retinas evaluated separately), exorbital lacrimal glands, Hardarian glands, Zymbal's glands)-Musculoskeletal-Gross necropsy; histopathology (skeletal muscle, sternum, femur/knee joint)-Skin/Connective Tissue-Gross pathology, histopathology
Duration and Exposure Route:	Inhalation-Gas-Duration: Subchronic (>30-90 days)-5-5-13-week(s)
Species:	Rat-Sprague-Dawley - [rat]-Both-Mouse-B6C3F1 - [mouse]-Both
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	5660612

Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
Metric 1:	Reporting Quality	High	All critical and important information were reported. Crf:CD BR rats (Sprague Dawley; age and source were specified; 10/sex/group) were exposed to 1,3-butadiene gas (CASRN, form, and source were reported) at 0, and 1,000 ppm. All animal husbandry details (cage type, number per cage, photoperiod, food and water availability, temperature, and humidity) were provided. Exposure methods and endpoint evaluation methods were described, and results were reported for at least one outcome of interest.
Domain 2: Selection and Performance			
Metric 2:	Allocation	High	Animals were allocated into groups using a stratified randomization procedure based on body weights.
Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not reported, but the endpoints were either not subjective, or the endpoints are from an initial histopathology review. No blinding was described for gross pathology or clinical signs.
Domain 3: Confounding / Variable Control			
Metric 4:	Confounding / Variable Control	Medium	A negative control group was included, but the nature of the control (e.g., air only) was not explicitly stated. The negative control responses were appropriate, where reported. Animal husbandry conditions were consistent across groups. There were no unusual changes in body weights; food consumption was recorded, and the authors indicated there were no changes. Reflex bradypnea was not monitored in an inhalation study, but there is no conclusive evidence that the test material is a respiratory irritant in animals.
Domain 4: Selective Reporting and Attrition			

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Study Citation:	Bevan, C., Stadler, J. C., Elliott, G. S., Frame, S. R., Baldwin, J. K., Leung, H. W., Moran, E., Panepinto, A. S. (1996). Subchronic toxicity of 4-vinylcyclohexene in rats and mice by inhalation exposure. <i>Fundamental and Applied Toxicology</i> 32(1):1-10.
Health Outcome(s) and Reported Health Effect(s):	Mortality-Mortality and moribundity-Nutritional/Metabolic-Weekly body weights; food consumption-Immune/Hematological-Hematology, spleen weight, gross necropsy, histopathology (bone marrow (sternal and femoral), mesenteric and mandibular lymph nodes, spleen, thymus)-Hepatic/Liver-Clinical chemistry (ALP, ALT, ASP, total protein, albumin, globulin, cholesterol, glucose, total bilirubin), liver weights, gross necropsy, histopathology-Renal/Kidney-Serum chemistry (BUN, creatinine, electrolytes), urinalysis, organ weight, gross necropsy, histopathology-Cardiovascular-Heart weight, gross necropsy, histopathology (aorta, heart)-Other (please specify below) (Endocrine)-Adrenal weights (rats only), gross necropsy, histopathology (pancreas, pituitary, adrenal glands)-Reproductive/Developmental-Organ weights: Testes, ovary (rats only); gross necropsy, histopathology (prostate, testes, epididymides, seminal vesicles, mammary gland, ovaries, uterus,vagina)-Neurological/Behavioral-Brain weight, gross pathology, histopathology (brain, spinal cord, sciatic nerve)-Gastrointestinal-Gross necropsy; histopathology (salivary glands, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, rectum gall-bladder (mice only))-Thyroid-Gross pathology; histopathology (thyroid, parathyroid)-Lung/Respiratory-Gross necropsy, histopathology (trachea, lungs, nose, larynx, pharynx)-Ocular/Sensory-Gross pathology; histopathology (eyes (retinas evaluated separately), exorbital lacrimal glands, Hardarian glands, Zymbal's glands)-Musculoskeletal-Gross necropsy; histopathology (skeletal muscle, sternum, femur/knee joint)-Skin/Connective Tissue-Gross pathology, histopathology
Duration and Exposure Route:	Inhalation-Gas-Duration: Subchronic (>30-90 days)-5-5-13-week(s)
Species:	Rat-Sprague-Dawley - [rat]-Both-Mouse-B6C3F1 - [mouse]-Both
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	5660612

Domain	Metric	Rating	Comments
	Metric 5: Selective Reporting and Attrition	Medium	There was no evidence of animal attrition. Except for histopathology results that reported incidences, the sample sizes used to generate other data were not specified in the data tables, so it cannot be determined whether any animals were excluded. Quantitative results for several endpoints were not reported, but there were qualitative statements describing the lack of observed effects. There is no indication of selective reporting.

Domain 5: Exposure Methods Sensitivity

Metric 6: Chemical administration and characterization	Low	The test substance was supplied by Exxon Chemical Co. and the purity was 99.9%. A certificate of analysis was not included, and the performing laboratory did not verify the test substance. The study referred to the test substance as both a gas and a vapor. Details on stability or storage were not provided. Exposure levels were analytically monitored by GC and the mean measured concentration was 980 ± 16 ppm. The exposure concentration used was based on data from previous studies. Animals were exposed whole body in 300 L chambers with an airflow of 60-70 liters/min (the number of air changes/hour was not reported). Test substance gas was diluted with filtered air to the desired concentration. It was not specified if the air was humidified.
Metric 7: Exposure timing, frequency, and duration	High	The exposure timing, frequency, and duration (6hrs/day, 5 days/week for 13 weeks) was consistent with standard guidelines for subchronic inhalation toxicity studies.

Domain 6: Outcome Measures and Results Display

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Study Citation:	Bevan, C., Stadler, J. C., Elliott, G. S., Frame, S. R., Baldwin, J. K., Leung, H. W., Moran, E., Panepinto, A. S. (1996). Subchronic toxicity of 4-vinylcyclohexene in rats and mice by inhalation exposure. <i>Fundamental and Applied Toxicology</i> 32(1):1-10.
Health Outcome(s) and Reported Health Effect(s):	Mortality-Mortality and moribundity-Nutritional/Metabolic-Weekly body weights; food consumption-Immune/Hematological-Hematology, spleen weight, gross necropsy, histopathology (bone marrow (sternal and femoral), mesenteric and mandibular lymph nodes, spleen, thymus)-Hepatic/Liver-Clinical chemistry (ALP, ALT, ASP, total protein, albumin, globulin, cholesterol, glucose, total bilirubin), liver weights, gross necropsy, histopathology-Renal/Kidney-Serum chemistry (BUN, creatinine, electrolytes), urinalysis, organ weight, gross necropsy, histopathology-Cardiovascular-Heart weight, gross necropsy, histopathology (aorta, heart)-Other (please specify below) (Endocrine)-Adrenal weights (rats only), gross necropsy, histopathology (pancreas, pituitary, adrenal glands)-Reproductive/Developmental-Organ weights: Testes, ovary (rats only); gross necropsy, histopathology (prostate, testes, epididymides, seminal vesicles, mammary gland, ovaries, uterus,vagina)-Neurological/Behavioral-Brain weight, gross pathology, histopathology (brain, spinal cord, sciatic nerve)-Gastrointestinal-Gross necropsy; histopathology (salivary glands, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, rectum gall-bladder (mice only))-Thyroid-Gross pathology; histopathology (thyroid, parathyroid)-Lung/Respiratory-Gross necropsy, histopathology (trachea, lungs, nose, larynx, pharynx)-Ocular/Sensory-Gross pathology; histopathology (eyes (retinas evaluated separately), exorbital lacrimal glands, Hardarian glands, Zymbal's glands)-Musculoskeletal-Gross necropsy; histopathology (skeletal muscle, sternum, femur/knee joint)-Skin/Connective Tissue-Gross pathology, histopathology
Duration and Exposure Route:	Inhalation-Gas-Duration: Subchronic (>30-90 days)-5-5-13-week(s)
Species:	Rat-Sprague-Dawley - [rat]-Both-Mouse-B6C3F1 - [mouse]-Both
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	5660612

Domain	Metric	Rating	Comments
	Metric 8: Endpoint sensitivity and specificity	Low	The study was conducted according to U.S. EPA TG 40CFR 798.2450 and was GLP compliant. The primary focus of the paper was to identify a dose-response for a different chemical (4-vinylcyclohexene), and to compare the results to 1,3-butadiene. The number of animals (20 total) and endpoints evaluated are consistent with guidelines and are generally sensitive to the outcomes of interest. Sampling was not specified for most outcomes, but all 10 animals/sex were examined for histopathology, and the numbers were sufficient to allow for statistical analysis. There are no concerns with the animals used. The study included only a single exposure concentration. Although the concentration tested was justified, the single concentration precludes the ability to identify a dose-response, thus, reducing the value of the study.
	Metric 9: Results presentation	Low	The methods of statistical analysis were clearly described and were appropriate for the datasets. Data the authors considered to be significant were generally reported quantitatively as incidences or as means \pm SD. For rats, a statement indicated there "was no compound-related mortality in rats." It is unclear if this means there were no deaths at all; mortality wasn't included in any of the data tables. Two deaths were noted for mice, but the sex was not specified. Body weight figures purportedly also included standard deviation, but the measures of variance are not discernable in the figure. Only relative, but not absolute organ wt. data for select organs were quantitatively provided. No individual animal data were provided and the reporting of histopathological results was limited to a table showing results for only select organs/tissues; severity was mentioned in the text.

Overall Quality Determination**Medium**

Study Citation: Bevan, C., Stadler, J. C., Elliott, G. S., Frame, S. R., Baldwin, J. K., Leung, H. W., Moran, E., Panepinto, A. S. (1996). Subchronic toxicity of 4-vinylcyclohexene in rats and mice by inhalation exposure. *Fundamental and Applied Toxicology* 32(1):1-10.

Health Outcome(s) and Reported Health Effect(s): Other (please specify below) (Clinical signs)-Unspecified clinical signs (results not reported)

Duration and Exposure Route: Inhalation-Gas-Duration: Subchronic (>30-90 days)-5-5-13-week(s)

Species: Rat-Sprague-Dawley - [rat]-Both-Mouse-B6C3F1 - [mouse]-Both

Chemical: 1,3-Butadiene- Parent compound

HERO ID: 5660612

Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	High	All critical and important information were reported. CrI:CD BR rats (Sprague Dawley; age and source were specified; 10/sex/group) were exposed to 1,3-butadiene gas (CASRN, form, and source were reported) at 0, and 1,000 ppm. All animal husbandry details (cage type, number per cage, photoperiod, food and water availability, temperature, and humidity) were provided. Exposure methods and endpoint evaluation methods were described, and results were reported for at least one outcome of interest.
Domain 2: Selection and Performance			
	Metric 2: Allocation	High	Animals were allocated into groups using a stratified randomization procedure based on body weights.
	Metric 3: Observational Bias / Blinding Changes	Medium	Blinding was not reported, but the endpoints were either not subjective, or the endpoints are from an initial histopathology review. No blinding was described for gross pathology or clinical signs.
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	Medium	A negative control group was included, but the nature of the control (e.g., air only) was not explicitly stated. The negative control responses were appropriate, where reported. Animal husbandry conditions were consistent across groups. There were no unusual changes in body weights; food consumption was recorded, and the authors indicated there were no changes. Reflex bradypnea was not monitored in an inhalation study, but there is no conclusive evidence that the test material is a respiratory irritant in animals.
Domain 4: Selective Reporting and Attrition			
	Metric 5: Selective Reporting and Attrition	Medium	There was no evidence of animal attrition. Except for histopathology results that reported incidences, the sample sizes used to generate other data were not specified in the data tables, so it cannot be determined whether any animals were excluded. Quantitative results for several endpoints were not reported, but there were qualitative statements describing the lack of observed effects. There is no indication of selective reporting; however, data for clinical signs were not reported.
Domain 5: Exposure Methods Sensitivity			

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Study Citation: Bevan, C., Stadler, J. C., Elliott, G. S., Frame, S. R., Baldwin, J. K., Leung, H. W., Moran, E., Panepinto, A. S. (1996). Subchronic toxicity of 4-vinylcyclohexene in rats and mice by inhalation exposure. *Fundamental and Applied Toxicology* 32(1):1-10.

Health Outcome(s) and Reported Health Effect(s): Other (please specify below) (Clinical signs)-Unspecified clinical signs (results not reported)

Duration and Exposure Route: Inhalation-Gas-Duration: Subchronic (>30-90 days)-5-5-13-week(s)

Species: Rat-Sprague-Dawley - [rat]-Both-Mouse-B6C3F1 - [mouse]-Both

Chemical: 1,3-Butadiene- Parent compound

HERO ID: 5660612

Domain	Metric	Rating	Comments
	Metric 6: Chemical administration and characterization	Low	The test substance was supplied by Exxon Chemical Co. and the purity was 99.9%. A certificate of analysis was not included, and the performing laboratory did not verify the test substance. The study referred to the test substance as both a gas and a vapor. Details on stability or storage were not provided. Exposure levels were analytically monitored by GC and the mean measured concentration was 980 ± 16 ppm. The exposure concentration used was based on data from previous studies. Animals were exposed whole body in 300 L chambers with an airflow of 60-70 liters/min (the number of air changes/hour was not reported). Test substance gas was diluted with filtered air to the desired concentration. It was not specified if the air was humidified.
	Metric 7: Exposure timing, frequency, and duration	High	The exposure timing, frequency, and duration (6hrs/day, 5 days/week for 13 weeks) was consistent with standard guidelines for subchronic inhalation toxicity studies.

Domain 6: Outcome Measures and Results Display

Metric 8: Endpoint sensitivity and specificity	Medium	The study was conducted according to U.S. EPA TG 40CFR 798.2450 and was GLP compliant. The primary focus of the paper was to identify a dose response for a different chemical (4-vinyl cyclohexene) and to compare the results to 1,3-butadiene. The number of animals (20 total) and endpoints evaluated (including clinical signs) are consistent with guidelines. The type of observations (cage-side or detailed) was not specified. Sampling could not be determined because the results were not reported. There are no concerns with the animals used. The study included only a single exposure concentration. Although the concentration tested was justified, the single concentration precludes the ability to identify a dose-response, thus, reducing the value of the study.
Metric 9: Results presentation	Uninformative	Results for clinical signs were not reported (only for the VCH analog).

Overall Quality Determination

Uninformative

Study Citation:	Brinkworth, M. H., Anderson, D., Hughes, J. A., Jackson, L. I., Yu, T. W., Nieschlag, E. (1998). Genetic effects of 1,3-butadiene on the mouse testis. Mutation Research 397(1):67-75.
Health Outcome(s) and Reported	Nutritional/Metabolic-Parental body weights-Reproductive/Developmental-Time to coition, proportion of males siring litters, number of females pregnant, total number of implants, number of live pups, number of dead implants (early deaths, late deaths, dead fetuses), number of living fetuses with external malformations. Sperm head and viability counts in males.-Other (please specify below) (Genotoxicity - Dominant lethality)-Dominant lethality
Health Effect(s):	
Duration and Exposure Route:	Inhalation-Gas-Duration: Subchronic (>30-90 days)-F0- premating (10 weeks)
Species:	Mouse-CD-1 - [mouse]-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	4934798

Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	Medium	All critical and most important information was provided. CD-1 mice (sex, source, and age were reported) were exposed to 1,3-butadiene (CASRN, source reported) via whole-body inhalation to the test material gas at 0, 12.5, or 125 ppm for 6 hrs/day, 5 days/week for 10 weeks (30 males/group). Most animal husbandry details (temperature, humidity, lighting, food and water availability) were specified. All endpoint evaluation methods were described. Quantitative or qualitative results were reported for at least one endpoint of interest. The missing information included animal starting body weights, parity, and the number of animals per cage during exposure. The purity of the test material was also not reported.
Domain 2: Selection and Performance			
	Metric 2: Allocation	Low	Males were randomly assigned to groups, but the method of randomization was not reported. The method of allocation of females to mating groups and whether animals were normalized to body weights was not specified.
	Metric 3: Observational Bias / Blinding Changes	Medium	The study did not report blinding or other methods/procedures for reducing observational bias; however, most of the outcomes were not subjective, and blinding was not required.
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	Low	Some details to determine whether there was confounding between groups were missing. Animal body weights were not reported and respiration rate was not monitored for an inhalation study. However, the test material is considered to be a respiratory irritant in humans (PubChem), but not animals. The study utilized an appropriate negative control (ambient air only). It is unclear if the negative control responses were appropriate. For example, the rate of late deaths was 0.014 and the abnormal fetuses occurred at 0.01 per live pup per pregnancy. In a previous study conducted under similar conditions, there were no late deaths in controls and no abnormalities. The authors noted that due to the observations in this study, no changes due to treatment reached statistical significance, as they did in the previous study. According to OECD TG 478, positive controls should always be used unless the testing laboratory has demonstrated proficiency in the conduct of the test. This laboratory referenced several previous studies using the same methods.
Domain 4: Selective Reporting and Attrition			

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Study Citation:	Brinkworth, M. H., Anderson, D., Hughes, J. A., Jackson, L. I., Yu, T. W., Nieschlag, E. (1998). Genetic effects of 1,3-butadiene on the mouse testis. Mutation Research 397(1):67-75.
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Parental body weights-Reproductive/Developmental-Time to coition, proportion of males siring litters, number of females pregnant, total number of implants, number of live pups, number of dead implants (early deaths, late deaths, dead fetuses), number of living fetuses with external malformations. Sperm head and viability counts in males.-Other (please specify below) (Genotoxicity - Dominant lethality)-Dominant lethality
Duration and Exposure Route:	Inhalation-Gas-Duration: Subchronic (>30-90 days)-F0- premating (10 weeks)
Species:	Mouse-CD-1 - [mouse]-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	4934798

Domain	Metric	Rating	Comments
	Metric 5: Selective Reporting and Attrition	High	There is no reporting of deaths in treated males and no evidence of animal attrition. Quantitative or qualitative statements were made for all endpoints, and quantitative data were provided for all exposure groups. The sample sizes were reported and were similar across groups. There is no evidence of selective reporting.

Domain 5: Exposure Methods Sensitivity

Metric 6: Chemical administration and characterization	Low	The test material was obtained from Aldrich Chemical Company. The CASRN was specified, but purity was not reported. Due to the age of the study, the exact product purchased cannot be located on the supplier's website. The performing laboratory did not analytically verify the test substance or report that it was supplied with a certificate of analysis. The study methods referred to the test material as "BD", but the title of the paper specified it was 1,3-butadiene. The test material was stored at -20 degrees for long-term storage and at 4 degrees between exposures. Exposure atmospheres were generated by diluting the test substances (presumably as a gas) in a stream of dry air at a constant flow rate. Animals were exposed whole body, and the number of mice per chamber was not specified. It was not explicitly stated if the chambers were static or dynamic and it is not entirely clear based on the information provided and there was no mention of air changes. The target exposure concentrations were reported and justified by the authors; the lowest concentration is equivalent to the maximum permitted occupational exposure limit in several countries. The atmospheres were analytically monitored but no analytical values were provided. It was specified by the authors that concentrations within 15% of the target were considered acceptable. The missing details could have a significant impact on the study results.
Metric 7: Exposure timing, frequency, and duration	High	The exposure timing, frequency, and duration were justified by the study authors and were based on results in previous studies.

Domain 6: Outcome Measures and Results Display

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Study Citation:	Brinkworth, M. H., Anderson, D., Hughes, J. A., Jackson, L. I., Yu, T. W., Nieschlag, E. (1998). Genetic effects of 1,3-butadiene on the mouse testis. Mutation Research 397(1):67-75.
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Parental body weights-Reproductive/Developmental-Time to coition, proportion of males siring litters, number of females pregnant, total number of implants, number of live pups, number of dead implants (early deaths, late deaths, dead fetuses), number of living fetuses with external malformations. Sperm head and viability counts in males.-Other (please specify below) (Genotoxicity - Dominant lethality)-Dominant lethality
Duration and Exposure Route:	Inhalation-Gas-Duration: Subchronic (>30-90 days)-F0- premating (10 weeks)
Species:	Mouse-CD-1 - [mouse]-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	4934798

Domain	Metric	Rating	Comments
	Metric 8: Endpoint sensitivity and specificity	Medium	This was a non-guideline dominant lethal study that had some deviations from current guidelines for this study type (OECD TG 478). A single mating occurred with 2 females for a maximum duration of 7 days. Typically, sequential weekly matings are conducted (e.g., 4 weekly matings are required after a 28-day exposure) so that all phases of spermatogenesis are evaluated. However, because the exposure duration for this study was so long (10 weeks) and the goal was simply to detect dominant lethality, then the single mating was likely appropriate. The study only included two exposure groups, plus a control but the concentrations and spacing were adequately justified by the authors. The endpoints were primarily focused on fetal death and were sensitive for the outcomes of interest and consistent with current guidelines. The outcome assessment methods were adequately described. Evaluations were conducted on all treatment groups. The animal model was appropriate, and animals were obtained from a commercial source. The sample size for the endpoints evaluated was sufficient.
	Metric 9: Results presentation	High	Statistical methods were adequately described for all endpoints. It was not specified that males were considered as the experimental unit. However, analysis of variance was conducted for most endpoints prior to conducting T-tests and some data were subjected to double arc sine transformation. Most results were quantitatively reported as incidences or means \pm SD, but negative findings (no effects observed) for parental body weight changes were qualitatively described in the text.

Overall Quality Determination**Medium**

Study Citation: Brinkworth, M. H., Anderson, D., Hughes, J. A., Jackson, L. I., Yu, T. W., Nieschlag, E. (1998). Genetic effects of 1,3-butadiene on the mouse testis. *Mutation Research* 397(1):67-75.

Health Outcome(s) and Reported Health Effect(s): Other (please specify below) (in vivo genotoxicity)-In testes: DNA damage (Comet assay) and unscheduled DNA synthesis (UDS)

Duration and Exposure Route: Inhalation-Gas-Duration: Subchronic (>30-90 days)-F0- premating (10 weeks)

Species: Mouse-CD-1 - [mouse]-Male

Chemical: 1,3-Butadiene- Parent compound

HERO ID: 4934798

Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	Medium	All critical and most important information was provided. CD-1 mice (sex, source, and age were reported) were exposed to 1,3-butadiene (CASRN, source reported) via whole-body inhalation to the test material gas at 0, 12.5, or 125 ppm for 6 hrs/day, 5 days/week for 10 weeks (30 males/group). Most animal husbandry details (temperature, humidity, lighting, food and water availability) were specified. All endpoint evaluation methods were described. Quantitative results were reported for the endpoints of interest. The missing information included animal starting body weights, parity, and the number of animals per cage during exposure. The purity of the test material was also not reported.
Domain 2: Selection and Performance			
	Metric 2: Allocation	Low	Males were randomly assigned to groups, but the method of randomization was not reported. The method of allocation of females to mating groups and whether animals were normalized to body weights was not specified.
	Metric 3: Observational Bias / Blinding Changes	Medium	The study did not report blinding or other methods/procedures for reducing observational bias; however, the outcomes were not subjective in nature or used computerized image analysis and blinding was not required.
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	Uninformative	Some details to determine whether there was confounding between groups were missing. Animal body weights were not reported and respiration rate was not monitored in an inhalation study. The test material is not considered to be a respiratory irritant in animals. The study utilized an appropriate negative control (ambient air only). The negative control responses were appropriate in most cases; however, for the UDS assay, a single control animal had high levels of 3H incorporation which heavily influenced the mean of the controls. This significantly impacts the ability to interpret the UDS data. No positive controls were included. According to OECD TG 486, the guideline for an in vivo unscheduled DNA synthesis test, concurrent positive controls are required. Additionally, based on OECD TG 480 (in vivo mammalian Alkaline Comet assay), positive controls, or demonstration of proficiency from the performing laboratory is also required.
Domain 4: Selective Reporting and Attrition			
	Metric 5: Selective Reporting and Attrition	Medium	There is no reporting of deaths in treated males and no evidence of animal attrition. Quantitative results were available for all endpoints. For some datasets, the sample size was 4 rather than 5 even though 5 animals/group were set aside for the experiments. Sperm data were derived from the same number of sperm counts.

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Study Citation: Brinkworth, M. H., Anderson, D., Hughes, J. A., Jackson, L. I., Yu, T. W., Nieschlag, E. (1998). Genetic effects of 1,3-butadiene on the mouse testis. *Mutation Research* 397(1):67-75.

Health Outcome(s) and Reported Health Effect(s): Other (please specify below) (in vivo genotoxicity)-In testes: DNA damage (Comet assay) and unscheduled DNA synthesis (UDS)

Duration and Exposure Route: Inhalation-Gas-Duration: Subchronic (>30-90 days)-F0- premating (10 weeks)

Species: Mouse-CD-1 - [mouse]-Male

Chemical: 1,3-Butadiene- Parent compound

HERO ID: 4934798

Domain	Metric	Rating	Comments
Domain 5: Exposure Methods Sensitivity			
	Metric 6: Chemical administration and characterization	Low	The test material was obtained from Aldrich Chemical Company. The CASRN was specified, but purity was not reported. Due to the age of the study, the exact product purchased cannot be located on the supplier's website. The performing laboratory did not analytically verify the test substance or report that it was supplied with a certificate of analysis. The study methods referred to the test material as "BD", but the title of the paper specified it was 1,3-butadiene. The test material was stored at -20 degrees for long-term storage and at 4 degrees between exposures. Exposure atmospheres were generated by diluting the test substances (presumably as a gas) in a stream of dry air at a constant flow rate. Animals were exposed whole body, and the number of mice per chamber was not specified. It was not explicitly stated if the chambers were static or dynamic and it is not entirely clear based on the information provided and there was no mention of air changes. The target exposure concentrations were reported and justified by the authors; the lowest concentration is equivalent to the maximum permitted occupational exposure limit in several countries. The atmospheres were analytically monitored but no analytical values were provided. It was specified by the authors that concentrations within 15% of the target were considered acceptable. The missing details could have a significant impact on the study results.
	Metric 7: Exposure timing, frequency, and duration	Low	The exposure timing, frequency, and duration were based on the primary focus of the study (reproductive effects), and animals were exposed for 10 weeks. The genotoxicity assays were an add-on to the main study. This metric was scored low because the 10-week exposure is inconsistent with current guidelines; however, the authors also conducted separate experiments (evaluated separately) where animals received single exposure.

Domain 6: Outcome Measures and Results Display

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Study Citation:	Brinkworth, M. H., Anderson, D., Hughes, J. A., Jackson, L. I., Yu, T. W., Nieschlag, E. (1998). Genetic effects of 1,3-butadiene on the mouse testis. Mutation Research 397(1):67-75.
Health Outcome(s) and Reported Health Effect(s):	Other (please specify below) (in vivo genotoxicity)-In testes: DNA damage (Comet assay) and unscheduled DNA synthesis (UDS)
Duration and Exposure Route:	Inhalation-Gas-Duration: Subchronic (>30-90 days)-F0- premating (10 weeks)
Species:	Mouse-CD-1 - [mouse]-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	4934798

Domain	Metric	Rating	Comments
	Metric 8: Endpoint sensitivity and specificity	Low	This was a non-guideline dominant lethal study that also conducted separate genotoxicity assays (Comet assay and UDS assay) on a subset of animals. Some methodological details were provided. The study cited a previous publication (Anderson et al. 1997). This reference was not freely accessible at the time of this review. The OECD guideline for the in vivo Comet assay specifies that the test is not appropriate to measure DNA strand breaks in mature germ cells, and that a positive result in testis samples is not necessarily reflective of germ cell damage. The current study did the assay in sperm, but no results were observed in the 10-week assay. There is no specification on tissues in the OECD TG 489 for UDS assays, although they are typically done using liver tissue. Evaluations were conducted on all treatment groups. The animal model was appropriate, and animals were obtained from a commercial source. The sample size for the endpoints evaluated was sufficient.
	Metric 9: Results presentation	High	Statistical methods were adequately described and data were presented as means \pm SD for all groups.

Overall Quality Determination

Uninformative

Study Citation:	Crouch, C. N., Pullinger, D. H., Gaunt, I. F. (1979). Inhalation toxicity studies with 1,3-butadiene - 2 3 month toxicity study in rats. Journal of Occupational and Environmental Hygiene 40(9):796-802.		
Health Outcome(s) and Reported Health Effect(s):	Mortality-Death-Other (please specify below) (Clinical signs)-Daily observations (salivation, reduction in grooming)		
Duration and Exposure Route:	Inhalation-Gas-Duration: Subchronic (>30-90 days)-5-6-13-week(s)		
Species:	Rat-Sprague-Dawley - [rat]-Both		
Chemical:	1,3-Butadiene- Parent compound		
HERO ID:	94760		
Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	High	All critical and Important information was reported. This included information on the test substance (name, purity, source); the test animals (source, strain, age, sex, and starting body weights); animal husbandry/housing conditions (number of animals per cage, temperature, humidity, diet, and water availability); the experimental design (frequency of exposure, number of animals per group and lifestage); endpoint evaluation methods, and quantitative results for at least one endpoint of interest. The only missing information was details on the light/dark cycle, which is not expected to have a significant impact on the study results.
Domain 2: Selection and Performance			
	Metric 2: Allocation	Medium	Animals were allocated via random selection (method not described) and were normalized by body weight.
	Metric 3: Observational Bias / Blinding Changes	Medium	Blinding was not specified; however, the endpoints were either simple measures, not subjective in nature, or blinding is not recommended or required (e.g., initial histopathology)
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	Medium	The study used filtered-air negative controls that were otherwise kept under identical exposure conditions. Due to the qualitative nature of data reporting, the appropriateness of the control responses cannot be determined. Reflex bradypnea was not tested in an inhalation study; however, there is insufficient information indicating the test substance is a respiratory irritant. No differences in body weights unrelated to exposure were described.
Domain 4: Selective Reporting and Attrition			
	Metric 5: Selective Reporting and Attrition	Medium	The study primarily reported results qualitatively with sometimes insufficient details for all exposure groups and durations.; however, results were mentioned for all of the outcomes specified in the study methods. Infection was evident (pneumonitis) in animals, but purportedly was not different across groups. 5 animals died, it was not reported which group(s) these animals belonged to.
Domain 5: Exposure Methods Sensitivity			

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Study Citation: Crouch, C. N., Pullinger, D. H., Gaunt, I. F. (1979). Inhalation toxicity studies with 1,3-butadiene - 2 3 month toxicity study in rats. *Journal of Occupational and Environmental Hygiene* 40(9):796-802.

Health Outcome(s) and Reported Health Effect(s): Mortality-Death-Other (please specify below) (Clinical signs)-Daily observations (salivation, reduction in grooming)

Duration and Exposure Route: Inhalation-Gas-Duration: Subchronic (>30-90 days)-5-6-13-week(s)

Species: Rat-Sprague-Dawley - [rat]-Both

Chemical: 1,3-Butadiene- Parent compound

HERO ID: 94760

Domain	Metric	Rating	Comments
	Metric 6: Chemical administration and characterization	Medium	The test substance was identified definitively, and the source was specified. The test substance was analytically verified during manufacturing; the purity was 99.2% and all impurities were reported. Different batches were obtained weekly throughout the study. The exposure concentrations were clearly reported, and the levels were justified by the study authors. The exposure route (whole-body inhalation) was appropriate. Details of the exposure chamber were cited to another publication (HERO 5616612) which was reviewed. This reference provided detailed information on the generation of the exposure atmospheres and chambers, as well as storage details. The flow rate was specified (1000 L/min), but the number of air changes per hour was not provided. The exposure concentrations were analytically monitored using appropriate methods and remained within 10% of nominal on 72 of the 75 days of exposure. Atmospheres were tested for the presence of the 4-vinyl-1-cyclohexane dimer and other impurities. Animals were acclimatized before exposure. No further details about the exposure methods were provided in the current study.
	Metric 7: Exposure timing, frequency, and duration	High	The exposure timing, frequency, and duration (6hrs/day, 5 days/week for 13-weeks) is consistent with OECD TG 413, and was appropriate for the purposes of the study.

Domain 6: Outcome Measures and Results Display

Metric 8: Endpoint sensitivity and specificity	High	The study used albino, hysterectomy derived, barrier maintained Sprague-Dawley rats. The rats were weanlings on arrival and males and females arrived in two separate batches (no further justification or details were provided). A subset of animals were killed prior to the start of the study to assure they were in good health. A sufficient number of animals were included to allow for interim sacrifices. The study tested 4 exposure groups in addition to controls, and the spacing was justified. Details of the outcome assessment methods were generally described, including the timing, sample size, and lists of measurements, and evaluations appeared to be consistent across groups. The endpoints were consistent with those normally assessed in a standard repeat-dose inhalation toxicity study (OECD 413) and conferred sufficient sensitivity for the purposes of the study. The Histopathology was conducted only in control and high dose animals, but this is acceptable according to OECD 413.
Metric 9: Results presentation	Uninformative	The text qualitatively stated that 5 animals died, but did not specify which groups they belonged to, or the time or cause of death. Clinical signs, noted to be dose-related, were described; but no incidences were reported. No statistical analysis was specified for either outcome. The lack of reporting details for precludes the ability to interpret the results for these outcomes.

Overall Quality Determination

Uninformative

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Study Citation: Crouch, C. N., Pullinger, D. H., Gaunt, I. F. (1979). Inhalation toxicity studies with 1,3-butadiene - 2 3 month toxicity study in rats. *Journal of Occupational and Environmental Hygiene* 40(9):796-802.

Health Outcome(s) and Reported Health Effect(s): Mortality-Death-Other (please specify below) (Clinical signs)-Daily observations (salivation, reduction in grooming)

Duration and Exposure Route: Inhalation-Gas-Duration: Subchronic (>30-90 days)-5-6-13-week(s)

Species: Rat-Sprague-Dawley - [rat]-Both

Chemical: 1,3-Butadiene- Parent compound

HERO ID: 94760

Domain	Metric	Rating	Comments
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Study Citation:	Crouch, C. N., Pullinger, D. H., Gaunt, I. F. (1979). Inhalation toxicity studies with 1,3-butadiene - 2 3 month toxicity study in rats. <i>Journal of Occupational and Environmental Hygiene</i> 40(9):796-802.
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Body weight, weight gain, food intake
Duration and Exposure Route:	Inhalation-Gas-Duration: Subchronic (>30-90 days)-5-6-13-week(s)
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	94760

Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	High	All critical and Important information was reported. This included information on the test substance (name, purity, source); the test animals (source, strain, age, sex, and starting body weights); animal husbandry/housing conditions (number of animals per cage, temperature, humidity, diet, and water availability); the experimental design (frequency of exposure, number of animals per group and lifestage); endpoint evaluation methods, and quantitative results for at least one endpoint of interest. The only missing information was details on the light/dark cycle, which is not expected to have a significant impact on the study results.
Domain 2: Selection and Performance			
	Metric 2: Allocation	Medium	Animals were allocated via random selection (method not described) and were normalized by body weight.
	Metric 3: Observational Bias / Blinding Changes	Medium	Blinding was not specified; however, the endpoints were either simple measures, not subjective in nature, or blinding is not recommended or required (e.g., initial histopathology)
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	Medium	The study used filtered-air negative controls that were otherwise kept under identical exposure conditions. Due to the qualitative nature of data reporting, the appropriateness of the control responses cannot be determined. Reflex bradypnea was not tested in an inhalation study; however, there is insufficient information indicating the test substance is a respiratory irritant. No differences in body weights unrelated to exposure were described.
Domain 4: Selective Reporting and Attrition			
	Metric 5: Selective Reporting and Attrition	Medium	The study primarily reported results qualitatively with sometimes insufficient details for all exposure groups and durations.; however, results were mentioned for all of the outcomes specified in the study methods. Infection was evident (pneumonitis) in animals, but purportedly was not different across groups. 5 animals died, it was not reported which group(s) these animals belonged to.
Domain 5: Exposure Methods Sensitivity			

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Study Citation:	Crouch, C. N., Pullinger, D. H., Gaunt, I. F. (1979). Inhalation toxicity studies with 1,3-butadiene - 2 3 month toxicity study in rats. <i>Journal of Occupational and Environmental Hygiene</i> 40(9):796-802.
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Body weight, weight gain, food intake
Duration and Exposure Route:	Inhalation-Gas-Duration: Subchronic (>30-90 days)-5-6-13-week(s)
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	94760

Domain	Metric	Rating	Comments
Metric 6:	Chemical administration and characterization	Medium	The test substance was identified definitively, and the source was specified. The test substance was analytically verified during manufacturing; the purity was 99.2% and all impurities were reported. Different batches were obtained weekly throughout the study. The exposure concentrations were clearly reported, and the levels were justified by the study authors. The exposure route (whole-body inhalation) was appropriate. Details of the exposure chamber were cited to another publication (HERO 5616612) which was reviewed. This reference provided detailed information on the generation of the exposure atmospheres and chambers, as well as storage details. The flow rate was specified (1000 L/min), but the number of air changes per hour was not provided. The exposure concentrations were analytically monitored using appropriate methods and remained within 10% of nominal on 72 of the 75 days of exposure. Atmospheres were tested for the presence of the 4-vinyl-1-cyclohexane dimer and other impurities. Animals were acclimatized before exposure. No further details about the exposure methods were provided in the current study.
Metric 7:	Exposure timing, frequency, and duration	High	The exposure timing, frequency, and duration (6hrs/day, 5 days/week for 13-weeks) is consistent with OECD TG 413, and was appropriate for the purposes of the study.

Domain 6: Outcome Measures and Results Display

Metric 8:	Endpoint sensitivity and specificity	High	The study used albino, hysterectomy derived, barrier maintained Sprague-Dawley rats. The rats were weanlings on arrival and males and females arrived in two separate batches (no further justification or details were provided). A subset of animals were killed prior to the start of the study to assure they were in good health. A sufficient number of animals were included to allow for interim sacrifices. The study tested 4 exposure groups in addition to controls, and the spacing was justified. Details of the outcome assessment methods were generally described, including the timing, sample size, and lists of measurements, and evaluations appeared to be consistent across groups. The endpoints were consistent with those normally assessed in a standard repeat-dose inhalation toxicity study (OECD 413) and conferred sufficient sensitivity for the purposes of the study. The Histopathology was conducted only in control and high dose animals, but this is acceptable according to OECD 413.
Metric 9:	Results presentation	Low	The endpoints were qualitatively described in the text and weekly body weights were shown in a figure in the absence of measures of variance, or an "n" (sample size). The only figure in the study showing data was for male body weights.; however females, not males were reported to have a significant change. It is unclear why the authors chose to show male mean body weights only. The text noted statistically significant changes in females, but no details on the methods of statistical analysis were provided.

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Study Citation: Crouch, C. N., Pullinger, D. H., Gaunt, I. F. (1979). Inhalation toxicity studies with 1,3-butadiene - 2 3 month toxicity study in rats. *Journal of Occupational and Environmental Hygiene* 40(9):796-802.

Health Outcome(s) and Reported Health Effect(s): Nutritional/Metabolic-Body weight, weight gain, food intake

Duration and Exposure Route: Inhalation-Gas-Duration: Subchronic (>30-90 days)-5-6-13-week(s)

Species: Rat-Sprague-Dawley - [rat]-Both

Chemical: 1,3-Butadiene- Parent compound

HERO ID: 94760

Domain	Metric	Rating	Comments
Overall Quality Determination		Medium	

Study Citation:	Crouch, C. N., Pullinger, D. H., Gaunt, I. F. (1979). Inhalation toxicity studies with 1,3-butadiene - 2 3 month toxicity study in rats. <i>Journal of Occupational and Environmental Hygiene</i> 40(9):796-802.
Health Outcome(s) and Reported Health Effect(s):	Gastrointestinal-Gross necropsy, histopathology (caecum, colon, esophagus, rectum, salivary glands, small intestine, stomach)-Musculoskeletal-Gross necropsy, histopathology (sternum, turbinate bones, femur, diaphragm)-Ocular/Sensory-Gross necropsy, histopathology (ears, eyes, optic nerve, harderian gland)-Skin/Connective Tissue-Gross necropsy, histopathology (skin)
Duration and Exposure Route:	Inhalation-Gas-Duration: Subchronic (>30-90 days)-5-6-13-week(s)
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	94760

Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	High	All critical and Important information was reported. This included information on the test substance (name, purity, source); the test animals (source, strain, age, sex, and starting body weights); animal husbandry/housing conditions (number of animals per cage, temperature, humidity, diet, and water availability); the experimental design (frequency of exposure, number of animals per group and lifestage); endpoint evaluation methods, and quantitative results for at least one endpoint of interest. The only missing information was details on the light/dark cycle, which is not expected to have a significant impact on the study results.
Domain 2: Selection and Performance			
	Metric 2: Allocation	Medium	Animals were allocated via random selection (method not described) and were normalized by body weight.
	Metric 3: Observational Bias / Blinding Changes	Medium	Blinding was not specified; however, the endpoints were either simple measures, not subjective in nature, or blinding is not recommended or required (e.g., initial histopathology)
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	Medium	The study used filtered-air negative controls that were otherwise kept under identical exposure conditions. Due to the qualitative nature of data reporting, the appropriateness of the control responses cannot be determined. Reflex bradypnea was not tested in an inhalation study; however, there is insufficient information indicating the test substance is a respiratory irritant. No differences in body weights unrelated to exposure were described.
Domain 4: Selective Reporting and Attrition			
	Metric 5: Selective Reporting and Attrition	Medium	The study primarily reported results qualitatively with sometimes insufficient details for all exposure groups and durations.; however, results were mentioned for all of the outcomes specified in the study methods. Infection was evident (pneumonitis) in animals, but purportedly was not different across groups. 5 animals died, it was not reported which group(s) these animals belonged to.
Domain 5: Exposure Methods Sensitivity			

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Study Citation:	Crouch, C. N., Pullinger, D. H., Gaunt, I. F. (1979). Inhalation toxicity studies with 1,3-butadiene - 2 3 month toxicity study in rats. Journal of Occupational and Environmental Hygiene 40(9):796-802.
Health Outcome(s) and Reported Health Effect(s):	Gastrointestinal-Gross necropsy, histopathology (caecum, colon, esophagus, rectum, salivary glands, small intestine, stomach)-Musculoskeletal-Gross necropsy, histopathology (sternum, turbinate bones, femur, diaphragm)-Ocular/Sensory-Gross necropsy, histopathology (ears, eyes, optic nerve, harderian gland)-Skin/Connective Tissue-Gross necropsy, histopathology (skin)
Duration and Exposure Route:	Inhalation-Gas-Duration: Subchronic (>30-90 days)-5-6-13-week(s)
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	94760

Domain	Metric	Rating	Comments
Metric 6:	Chemical administration and characterization	Medium	The test substance was identified definitively, and the source was specified. The test substance was analytically verified during manufacturing; the purity was 99.2% and all impurities were reported. Different batches were obtained weekly throughout the study. The exposure concentrations were clearly reported, and the levels were justified by the study authors. The exposure route (whole-body inhalation) was appropriate. Details of the exposure chamber were cited to another publication (HERO 5616612) which was reviewed. This reference provided detailed information on the generation of the exposure atmospheres and chambers, as well as storage details. The flow rate was specified (1000 L/min), but the number of air changes per hour was not provided. The exposure concentrations were analytically monitored using appropriate methods and remained within 10% of nominal on 72 of the 75 days of exposure. Atmospheres were tested for the presence of the 4-vinyl-1-cyclohexane dimer and other impurities. Animals were acclimatized before exposure. No further details about the exposure methods were provided in the current study.
Metric 7:	Exposure timing, frequency, and duration	High	The exposure timing, frequency, and duration (6hrs/day, 5 days/week for 13-weeks) is consistent with OECD TG 413, and was appropriate for the purposes of the study.
Domain 6: Outcome Measures and Results Display			
Metric 8:	Endpoint sensitivity and specificity	High	The study used albino, hysterectomy derived, barrier maintained Sprague-Dawley rats. The rats were weanlings on arrival and males and females arrived in two separate batches (no further justification or details were provided). A subset of animals were killed prior to the start of the study to assure they were in good health. A sufficient number of animals were included to allow for interim sacrifices. The study tested 4 exposure groups in addition to controls, and the spacing was justified. Details of the outcome assessment methods were generally described, including the timing, sample size, and lists of measurements, and evaluations appeared to be consistent across groups. The endpoints were consistent with those normally assessed in a standard repeat-dose inhalation toxicity study (OECD 413) and conferred sufficient sensitivity for the purposes of the study. The Histopathology was conducted only in control and high dose animals, but this is acceptable according to OECD 413.
Metric 9:	Results presentation	Medium	A qualitative statement stating that the "incidence and severity of histological findings was similar to those in the control group" was provided.

Overall Quality Determination**Medium**

Study Citation:	Crouch, C. N., Pullinger, D. H., Gaunt, I. F. (1979). Inhalation toxicity studies with 1,3-butadiene - 2 3 month toxicity study in rats. <i>Journal of Occupational and Environmental Hygiene</i> 40(9):796-802.
Health Outcome(s) and Reported Health Effect(s):	Immune/Hematological-Hematology (packed cell volume, hemoglobin, RBC, WBC count, WBC differential, platelets, reticulocytes), erythrocyte analysis (cholinesterase, osmotic fragility, sulphhydril, reduced sulphhydril), neutrophil phagocytosis, prothrombin time. Spleen weights, gross necropsy, histopathology (lymph nodes, spleen, thymus)-Renal/Kidney-Urinalysis, serum urea, kidney weights, gross examinations, histopathology (kidney, bladder)-Hepatic/Liver-Clinical chemistry (glucose, total protein, albumin, glutamic oxaloacetic transaminase, and glutamic pyruvic transaminase activity, ALP), liver weight, gross examinations, and histopathology-Neurological/Behavioral-Brain weight, neuromuscular function test (rotating cone), brain cholinesterase activity, gross necropsy, histopathology (sciatic nerve)-Other (please specify below) (Endocrine)-Organ weights (adrenal, pituitary), gross necropsy, histopathology (adipose tissue, pancreas, pituitary)-Reproductive/Developmental-Organ weights (gonads), gross necropsy, histopathology (testes, ovary, epididymis, prostate, seminal vesicles, vagina, uterus)-Cardiovascular-Heart weight, gross necropsy, histopathology (aorta, heart)-Thyroid-Thyroid weight, gross necropsy, histopathology (thyroid, parathyroid)-Lung/Respiratory-Lung weight, gross necropsy, histopathology (lungs, larynx, trachea, nasal turbinates)
Duration and Exposure Route:	Inhalation-Gas-Duration: Subchronic (>30-90 days)-5-6-13-week(s)
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	94760

Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	High	All critical and Important information was reported. This included information on the test substance (name, purity, source); the test animals (source, strain, age, sex, and starting body weights); animal husbandry/housing conditions (number of animals per cage, temperature, humidity, diet, and water availability); the experimental design (frequency of exposure, number of animals per group and lifestage); endpoint evaluation methods, and quantitative results for at least one endpoint of interest. The only missing information was details on the light/dark cycle, which is not expected to have a significant impact on the study results.
Domain 2: Selection and Performance			
	Metric 2: Allocation	Medium	Animals were allocated via random selection (method not described) and were normalized by body weight.
	Metric 3: Observational Bias / Blinding Changes	Low	Blinding was not specified, and one endpoint in this outcome of interest (a neuromuscular function test) is subjective in nature and should have been performed in a blinding fashion. Blinding is not required for other endpoints measured for this outcome.
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	Medium	The study used filtered-air negative controls that were otherwise kept under identical exposure conditions. Due to the qualitative nature of data reporting, the appropriateness of the control responses cannot be determined. Reflex bradypnea was not tested in an inhalation study; however, there is insufficient information indicating the test substance is a respiratory irritant. No differences in body weights unrelated to exposure were described.
Domain 4: Selective Reporting and Attrition			

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Study Citation:	Crouch, C. N., Pullinger, D. H., Gaunt, I. F. (1979). Inhalation toxicity studies with 1,3-butadiene - 2 3 month toxicity study in rats. <i>Journal of Occupational and Environmental Hygiene</i> 40(9):796-802.
Health Outcome(s) and Reported Health Effect(s):	Immune/Hematological-Hematology (packed cell volume, hemoglobin, RBC, WBC count, WBC differential, platelets, reticulocytes), erythrocyte analysis (cholinesterase, osmotic fragility, sulphhydril, reduced sulphhydril), neutrophil phagocytosis, prothrombin time. Spleen weights, gross necropsy, histopathology (lymph nodes, spleen, thymus)-Renal/Kidney-Urinalysis, serum urea, kidney weights, gross examinations, histopathology (kidney, bladder)-Hepatic/Liver-Clinical chemistry (glucose, total protein, albumin, glutamic oxaloacetic transaminase, and glutamic pyruvic transaminase activity, ALP), liver weight, gross examinations, and histopathology-Neurological/Behavioral-Brain weight, neuromuscular function test (rotating cone), brain cholinesterase activity, gross necropsy, histopathology (sciatic nerve)-Other (please specify below) (Endocrine)-Organ weights (adrenal, pituitary), gross necropsy, histopathology (adipose tissue, pancreas, pituitary)-Reproductive/Developmental-Organ weights (gonads), gross necropsy, histopathology (testes, ovary, epididymis, prostate, seminal vesicles, vagina, uterus)-Cardiovascular-Heart weight, gross necropsy, histopathology (aorta, heart)-Thyroid-Thyroid weight, gross necropsy, histopathology (thyroid, parathyroid)-Lung/Respiratory-Lung weight, gross necropsy, histopathology (lungs, larynx, trachea, nasal turbinates)
Duration and Exposure Route:	Inhalation-Gas-Duration: Subchronic (>30-90 days)-5-6-13-week(s)
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	94760

Domain	Metric	Rating	Comments
Metric 5:	Selective Reporting and Attrition	Medium	The study primarily reported results qualitatively with sometimes insufficient details for all exposure groups and durations.; however, results were mentioned for all of the outcomes specified in the study methods. Infection was evident (pneumonitis) in animals, but purportedly was not different across groups. 5 animals died, it was not reported which group(s) these animals belonged to.
Domain 5: Exposure Methods Sensitivity			
Metric 6:	Chemical administration and characterization	Medium	The test substance was identified definitively, and the source was specified. The test substance was analytically verified during manufacturing; the purity was 99.2% and all impurities were reported. Different batches were obtained weekly throughout the study. The exposure concentrations were clearly reported, and the levels were justified by the study authors. The exposure route (whole-body inhalation) was appropriate. Details of the exposure chamber were cited to another publication (HERO 5616612) which was reviewed. This reference provided detailed information on the generation of the exposure atmospheres and chambers, as well as storage details. The flow rate was specified (1000 L/min), but the number of air changes per hour was not provided. The exposure concentrations were analytically monitored using appropriate methods and remained within 10% of nominal on 72 of the 75 days of exposure. Atmospheres were tested for the presence of the 4-vinyl-1-cyclohexane dimer and other impurities. Animals were acclimatized before exposure. No further details about the exposure methods were provided in the current study.
Metric 7:	Exposure timing, frequency, and duration	High	The exposure timing, frequency, and duration (6hrs/day, 5 days/week for 13-weeks) is consistent with OECD TG 413, and was appropriate for the purposes of the study.

Domain 6: Outcome Measures and Results Display

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Study Citation:	Crouch, C. N., Pullinger, D. H., Gaunt, I. F. (1979). Inhalation toxicity studies with 1,3-butadiene - 2 3 month toxicity study in rats. <i>Journal of Occupational and Environmental Hygiene</i> 40(9):796-802.
Health Outcome(s) and Reported Health Effect(s):	Immune/Hematological-Hematology (packed cell volume, hemoglobin, RBC, WBC count, WBC differential, platelets, reticulocytes), erythrocyte analysis (cholinesterase, osmotic fragility, sulphhydril, reduced sulphhydril), neutrophil phagocytosis, prothrombin time. Spleen weights, gross necropsy, histopathology (lymph nodes, spleen, thymus)-Renal/Kidney-Urinalysis, serum urea, kidney weights, gross examinations, histopathology (kidney, bladder)-Hepatic/Liver-Clinical chemistry (glucose, total protein, albumin, glutamic oxaloacetic transaminase, and glutamic pyruvic transaminase activity, ALP), liver weight, gross examinations, and histopathology-Neurological/Behavioral-Brain weight, neuromuscular function test (rotating cone), brain cholinesterase activity, gross necropsy, histopathology (sciatic nerve)-Other (please specify below) (Endocrine)-Organ weights (adrenal, pituitary), gross necropsy, histopathology (adipose tissue, pancreas, pituitary)-Reproductive/Developmental-Organ weights (gonads), gross necropsy, histopathology (testes, ovary, epididymis, prostate, seminal vesicles, vagina, uterus)-Cardiovascular-Heart weight, gross necropsy, histopathology (aorta, heart)-Thyroid-Thyroid weight, gross necropsy, histopathology (thyroid, parathyroid)-Lung/Respiratory-Lung weight, gross necropsy, histopathology (lungs, larynx, trachea, nasal turbinates)
Duration and Exposure Route:	Inhalation-Gas-Duration: Subchronic (>30-90 days)-5-6-13-week(s)
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	94760

Domain	Metric	Rating	Comments
Metric 8:	Endpoint sensitivity and specificity	High	The study used albino, hysterectomy derived, barrier maintained Sprague-Dawley rats. The rats were weanlings on arrival and males and females arrived in two separate batches (no further justification or details were provided). A subset of animals were killed prior to the start of the study to assure they were in good health. A sufficient number of animals were included to allow for interim sacrifices. The study tested 4 exposure groups in addition to controls, and the spacing was justified. Details of the outcome assessment methods were generally described, including the timing, sample size, and lists of measurements, and evaluations appeared to be consistent across groups. The endpoints were consistent with those normally assessed in a standard repeat-dose inhalation toxicity study (OECD 413) and conferred sufficient sensitivity for the purposes of the study. The Histopathology was conducted only in control and high dose animals, but this is acceptable according to OECD 413.
Metric 9:	Results presentation	Uninformative	Qualitative statements for organ weights, gross necropsy, and histopathological results were provided. A generalized statement indicated that there were statistically significant organ weights that were not considered to be treatment-related, but the text did not specify which organs or groups these were from, and no methods for statistical analysis were provided. Qualitative statements for macroscopic and microscopic examinations were primarily to note the absence of any observed effects. The text noted that there were some group differences in the rotating cone test, but did not provide the data. The authors considered the changes to be not treatment-related, but this cannot be verified. No statistical methods were specified.

Overall Quality Determination**Uninformative**

Study Citation:	IBT Labs, (1977). Report to Tracor Jitco, Inc: Subchronic inhalation study with 1,3-butadiene (C50602) in B6C3F1 mice.		
Health Outcome(s) and Reported Health Effect(s):	Mortality-Mortality-Other (please specify below) (Clinical signs)-Clinical signs of toxicity-Nutritional/Metabolic-Body weight-Renal/Kidney-Histopathology on kidney and urinary bladder-Lung/Respiratory-Histopathology on lung and nasal cavity-Skin/Connective Tissue-Histopathology on skin-Hepatic/Liver-Histopathology on liver-Gastrointestinal-Histopathology on duodenum and gall bladder-Other (please specify below) (Endocrine)-Histopathology on adrenal gland-Neurological/Behavioral-Histopathology on brain-Immune/Hematological-Histopathology on bone marrow		
Duration and Exposure Route:	Inhalation-Vapor-Duration: Subchronic (>30-90 days)-5-6-13-week(s)		
Species:	Mouse-B6C3F1 - [mouse]-Both		
Chemical:	1,3-Butadiene- Parent compound		
HERO ID:	11273565		
Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
Metric 1: Reporting Quality	Medium	The test substance was identified as 1,3-Butadiene. The source (Phillips Chemical Company, Phillips, TX). The purity was not reported, and this information could not be found on the company's website. Test animal species, strain, age, source, initial body weights, and sex were reported. Husbandry conditions were not fully reported (temperature and humidity of room were not reported). Light cycle was a 12-hour on/off. Food and water were available ad libitum. Animals were individually housed. The dose levels, frequency, duration, and route of exposure were reported. The target and actual concentrations were reported. Endpoint evaluation methods were reported along with quantitative data. All critical information is provided and although some important information is missing, the missing information is not expected to significantly impact the study evaluation.	
Domain 2: Selection and Performance			
Metric 2: Allocation	High	Animals were weighed and randomly assigned into groups using a computer randomization program.	
Metric 3: Observational Bias / Blinding Changes	Medium	Blinding or other measures to reduce observational bias were not reported; however, the endpoints are either not subjective in nature (mortality, body weights) or assessed clinical signs or initial histopathology.	
Domain 3: Confounding / Variable Control			
Metric 4: Confounding / Variable Control	Low	A sham-exposed negative control group was included. Body weights were reported, but food and water intake were not. The chemical propylene was also tested in the same room, therefore there is potential for cross-contamination of the air, and inadvertent exposure of animals to propylene. The study reports controls were moved to a different room for day 26-33 and all animals were moved to a different room on day 75-76 (reasoning not reported). This change in rooms may confound results. Respiratory rate was not reported but the chemical is not expected to be a respiratory irritant.	
Domain 4: Selective Reporting and Attrition			
Metric 5: Selective Reporting and Attrition	Medium	Mortality was reported and all animals were accounted for.	
Domain 5: Exposure Methods Sensitivity			

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Study Citation:	IBT Labs, (1977). Report to Tracor Jitco, Inc: Subchronic inhalation study with 1,3-butadiene (C50602) in B6C3F1 mice.
Health Outcome(s) and Reported Health Effect(s):	Mortality-Mortality-Other (please specify below) (Clinical signs)-Clinical signs of toxicity-Nutritional/Metabolic-Body weight-Renal/Kidney-Histopathology on kidney and urinary bladder-Lung/Respiratory-Histopathology on lung and nasal cavity-Skin/Connective Tissue-Histopathology on skin-Hepatic/Liver-Histopathology on liver-Gastrointestinal-Histopathology on duodenum and gall bladder-Other (please specify below) (Endocrine)-Histopathology on adrenal gland-Neurological/Behavioral-Histopathology on brain-Immune/Hematological-Histopathology on bone marrow
Duration and Exposure Route:	Inhalation-Vapor-Duration: Subchronic (>30-90 days)-5-6-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	11273565

Domain	Metric	Rating	Comments
	Metric 6: Chemical administration and characterization	Low	The purity of the test substance was not reported and could not be found on the source company's website. Target concentration and analytical concentrations were reported. The generation of test substance vapor was adequately reported. Storage of test substance was not reported. Animals were exposed in a whole-body dynamic inhalation chamber, thus the possibility of test substance deposition on fur (and ingestion during grooming) is a concern. The number of air changes/hour was not reported.
	Metric 7: Exposure timing, frequency, and duration	Low	The study reports animals were exposed 6 hours/day for 13 weeks for a total of 64 days. It does not report how many days/week animals were exposed.

Domain 6: Outcome Measures and Results Display

Metric 8: Endpoint sensitivity and specificity	High	The number of animals/group was appropriate. The outcome methodology was sensitive to outcome of interest. Animals were assessed consistently across study groups. Histology was performed on controls, high concentration groups and any animal that died. No compound-related histology changes were seen in the high concentration group, so that appropriate. Justification for the selection of concentration testes was not reported, however significant mortality was seen at the higher concentrations in males.
Metric 9: Results presentation	Uninformative	Data are fully reported for mortality, clinical signs, body weight and histopathology. This metric is assigned uninformative because it was a 1977/78 IBT study. Data from IBT Labs from 1960-78 is considered unreliable and cannot be used.

Overall Quality Determination

Uninformative

Study Citation:	IBT Labs, (1977). Report to Tracor Jitco, Inc: Subchronic inhalation study with 1,3-butadiene (C50602) in B6C3F1 mice.
Health Outcome(s) and Reported Health Effect(s):	Mortality-Mortality-Other (please specify below) (Clinical signs)-Clinical signs of toxicity-Nutritional/Metabolic-Body weight-Renal/Kidney-Histopathology on kidney and urinary bladder-Lung/Respiratory-Histopathology on lung and nasal cavity-Skin/Connective Tissue-Histopathology on skin-Reproductive/Developmental-Histopathology on penis-Hepatic/Liver-Histopathology on liver
Duration and Exposure Route:	Inhalation-Vapor-Duration: Subchronic (>30-90 days)-5-6-13-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	11273565

Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	Medium	The test substance was identified as 1,3-Butadiene. The source (Phillips Chemical Company, Phillips, TX). The purity was not reported, and this information could not be found on the company's website. Test animal species, strain, age, source, initial body weights, and sex were reported. Husbandry conditions were not fully reported (temperature and humidity of room were not reported). Light cycle was a 12-hour on/off. Food and water were available ad libitum. Animals were individually housed. The dose levels, frequency, duration, and route of exposure were reported. The target and actual concentrations were reported. Endpoint evaluation methods were reported along with quantitative data. All critical information is provided and although some important information is missing, the missing information is not expected to significantly impact the study evaluation.
Domain 2: Selection and Performance			
	Metric 2: Allocation	High	Animals were weighed and randomly assigned into groups using a computer randomization program.
	Metric 3: Observational Bias / Blinding Changes	Medium	Blinding or other measures to reduce observational bias were not reported; however, the endpoints are either not subjective in nature (mortality, body weights) or assessed clinical signs or initial histopathology.
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	Low	A sham-exposed negative control group was included. Body weights were reported, but food and water intake were not. The chemical propylene was also tested in the same room, therefore there is potential for cross-contamination of the air, and inadvertent exposure of animals to propylene. The study reports controls were moved to a different room for day 26-33 and all animals were moved to a different room on day 75-76 (reasoning not reported). This change in rooms may confound results. Respiratory rate was not reported but the chemical is not expected to be a respiratory irritant.
Domain 4: Selective Reporting and Attrition			
	Metric 5: Selective Reporting and Attrition	Medium	Mortality was reported and all animals were accounted for.
Domain 5: Exposure Methods Sensitivity			

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Study Citation: IBT Labs, (1977). Report to Tracor Jitco, Inc: Subchronic inhalation study with 1,3-butadiene (C50602) in B6C3F1 mice.

Health Outcome(s) and Reported Health Effect(s): Mortality-Mortality-Other (please specify below) (Clinical signs)-Clinical signs of toxicity-Nutritional/Metabolic-Body weight-Renal/Kidney-Histopathology on kidney and urinary bladder-Lung/Respiratory-Histopathology on lung and nasal cavity-Skin/Connective Tissue-Histopathology on skin-Reproductive/Developmental-Histopathology on penis-Hepatic/Liver-Histopathology on liver

Duration and Exposure Route: Inhalation-Vapor-Duration: Subchronic (>30-90 days)-5-6-13-week(s)

Species: Mouse-B6C3F1 - [mouse]-Male

Chemical: 1,3-Butadiene- Parent compound

HERO ID: 11273565

Domain	Metric	Rating	Comments
	Metric 6: Chemical administration and characterization	Low	The purity of the test substance was not reported and could not be found on the source company's website. Target concentration and analytical concentrations were reported. The generation of test substance vapor was adequately reported. Storage of test substance was not reported. Animals were exposed in a whole-body dynamic inhalation chamber, thus the possibility of test substance deposition on fur (and ingestion during grooming) is a concern. The number of air changes/hour was not reported.
	Metric 7: Exposure timing, frequency, and duration	Low	The study reports animals were exposed 6 hours/day for 13 weeks for a total of 63 days. It does not report how many days/week animals were exposed.

Domain 6: Outcome Measures and Results Display

Metric 8: Endpoint sensitivity and specificity	High	The number of animals/group was appropriate. The outcome methodology was sensitive to outcome of interest. Animals were assessed consistently across study groups. The concentration was chosen because of the high mortality seen at this concentration in an earlier study.
Metric 9: Results presentation	Uninformative	Data are fully reported for mortality, clinical signs, body weight and histopathology. Mortality counts for high-dose males differed in tables from the text. This metric is assigned uninformative because it was a 1977/78 IBT study. Data from IBT Labs from 1960-78 is considered unreliable and cannot be used.

Overall Quality Determination

Uninformative

Study Citation:	NTP, (1993). NTP Toxicology and Carcinogenesis Studies of 1,3-Butadiene (CAS No. 106-99-0) in B6C3F1 Mice (Inhalation Studies). National Toxicology Program Technical Report Series 434:1-389.		
Health Outcome(s) and Reported	Mortality-Survival-Nutritional/Metabolic-Body weights		
Health Effect(s):			
Duration and Exposure Route:	Inhalation-Vapor-Duration: Chronic (>90 days)-5-6-52-week(s)-Inhalation-Vapor-Duration: Subchronic (>30-90 days)-5-6-13-week(s)		
Species:	Mouse-B6C3F1 - [mouse]-Male		
Chemical:	1,3-Butadiene- Parent compound		
HERO ID:	1419645		
Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
Metric 1: Reporting Quality		High	Test substance identity, source and purity were reported, and the identity and purity were confirmed by infrared spectroscopy and gas chromatography. The inhalation chamber was described in detail. Test animal species, sex, strain, starting age and source were reported. Starting body weights are not reported in the methods but are presented in the results. Animal housing conditions that included number of animals per cage, food and water availability, temperature, humidity, day/night cycle, and room air changes per hour were reported. The study design is described in detail and endpoint assessment methods were reported.
Domain 2: Selection and Performance			
Metric 2: Allocation		High	Animals were randomly assigned to groups using body weight as a blocking variable in the XYBION PATH/TOX system. Animals were randomly assigned to groups using body weight as a blocking variable in the XYBION PATH/TOX system.
Metric 3: Observational Bias / Blinding Changes		Medium	No measures to reduce observational bias were described, but measured endpoints were objective in nature or included initial histopathology and were not subject to observational bias. Histopathology was performed by an independent pathology quality assessment laboratory, but it is not stated whether assessors did a secondary blinded review or only did initial histopathology.
Domain 3: Confounding / Variable Control			
Metric 4: Confounding / Variable Control		High	An appropriate vehicle control was used, and additional historical controls were used to evaluate the effects for certain neoplastic lesions. The study measured and controlled for relevant confounding factors, and confounding bias is unlikely to be a problem in this study.
Domain 4: Selective Reporting and Attrition			
Metric 5: Selective Reporting and Attrition		Medium	The authors report 1 accidental death and many natural deaths and exposure-related deaths over the course of the study. The natural deaths were unrelated to the exposure and are unlikely to significantly bias the results of the study. All outcomes described in the methods were reported in the results.
Domain 5: Exposure Methods Sensitivity			

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Study Citation:	NTP, (1993). NTP Toxicology and Carcinogenesis Studies of 1,3-Butadiene (CAS No. 106-99-0) in B6C3F1 Mice (Inhalation Studies). National Toxicology Program Technical Report Series 434:1-389.		
Health Outcome(s) and Reported Health Effect(s):	Mortality-Survival-Nutritional/Metabolic-Body weights		
Duration and Exposure Route:	Inhalation-Vapor-Duration: Chronic (>90 days)-5-6-52-week(s)-Inhalation-Vapor-Duration: Subchronic (>30-90 days)-5-6-13-week(s)		
Species:	Mouse-B6C3F1 - [mouse]-Male		
Chemical:	1,3-Butadiene- Parent compound		
HERO ID:	1419645		

Domain	Metric	Rating	Comments
	Metric 6: Chemical administration and characterization	Medium	The authors performed independent analytical verification of the test substance identity and purity and monitored exposure chamber concentrations during the exposure. Exposure characterization was redone every 3 months and the authors reported <5% variability in chamber concentrations. There are no concerns regarding the exposure chamber used. Test substance storage conditions were not described, but the authors state that 7 different lots of the chemical were used over the 2-year exposure period, which may have mitigated the potential effects of chemical instability over the course of the experiment.
	Metric 7: Exposure timing, frequency, and duration	High	The exposure duration and frequency are sensitive to detect the endpoints of interest and does include the critical window of sensitivity for detecting health effects from chronic-duration exposures.

Domain 6: Outcome Measures and Results Display

Metric 8: Endpoint sensitivity and specificity	Low	The species is appropriate and there are no concerns regarding the specificity or sensitivity of the outcome assessment protocols. 50 animals were used for the main study groups, which is informative for detecting the endpoints of interest at chronic durations. The different exposure concentrations in this study were assessed at different times in order to test the hypothesis that effects would be directly related to the product of the exposure concentration times the duration of exposure. While this hypothesis has scientific merit, the inconsistency between exposure durations at different doses makes this experiment difficult to interpret for the sake of evaluating dose-response.
Metric 9: Results presentation	Medium	The results presentation generally includes full quantitative presentation in figures and tables and qualitative descriptions in the text. Notably, measures of variance for continuous endpoints are omitted from figures and tables, which may have a minor impact on the ability to interpret the results.

Overall Quality Determination**Medium**

Study Citation:	NTP, (1993). NTP Toxicology and Carcinogenesis Studies of 1,3-Butadiene (CAS No. 106-99-0) in B6C3F1 Mice (Inhalation Studies). National Toxicology Program Technical Report Series 434:1-389.
Health Outcome(s) and Reported Health Effect(s):	Cancer/Carcinogenesis-Malignant lymphoma, histiocytic sarcoma, cardiac hemangio- sarcoma; harderian gland adenoma, hepatocellular adenoma and carcinoma, alveolarbronchiolar adenoma and carcinoma; mammary gland carcinoma, adenoacanthoma, and malignant mixed tumor, benign and malignant ovarian granulosa cell tumor; and forestomach squamous cell papilloma and carcinoma, intestinal carcinomas, renal tubule adenomas, skin sarcomas, Zymbal's gland adenomas and carcinomas, lymphocytic lymphomas-Immune/Hematological-Histopathology: bone marrow, thymus, lymph nodes, spleen. Erythrocyte counts, hemoglobin concentration, packed red cell volume, mean erythrocyte volume, Organ weight: spleen and thymus-Reproductive/Developmental-Histopathology: testis, ovaries, uterus, mammary gland, seminal vesicle, epididymides, prostate gland, Organ weight: right testis-Gastrointestinal-Histopathology: stomach, small intestine, large intestine, gallbladder, salivary gland, esophagus-Lung/Respiratory-Histopathology: trachea, larynx, lung, pharynx, nose, Organ weight: lungs-Neurological/Behavioral-Histopathology: Brain, Organ weight: brain-Renal/Kidney-Histopathology: kidney. Creatine kinase in serum. Organ weight: right kidney-Hepatic/Liver-Histopathology: liver. Lactate dehydrogenase in serum, Organ weight: liver-Cardiovascular-Histopathology: Heart, Organ weight: heart-Musculoskeletal-Histopathology: sternebrae-Other (please specify below) (Endocrine)-Histopathology: Thyroid, parathyroid gland, pancreas, adrenal gland-Ocular/Sensory-Histopathology: Harderian gland Inhalation-Vapor-Duration: Chronic (>90 days)-5-6-52-week(s)-Inhalation-Vapor-Duration: Subchronic (>30-90 days)-5-6-13-week(s)
Duration and Exposure Route:	
Species:	Mouse-B6C3F1 - [mouse]-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	1419645

Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	High	Test substance identity, source and purity were reported, and the identity and purity were confirmed by infrared spectroscopy and gas chromatography. The inhalation chamber was described in detail. Test animal species, sex, strain, starting age and source were reported. Starting body weights are not reported in the methods but are presented in the results. Animal housing conditions that included number of animals per cage, food and water availability, temperature, humidity, day/night cycle, and room air changes per hour were reported. The study design is described in detail and endpoint assessment methods were reported.
Domain 2: Selection and Performance			
	Metric 2: Allocation	High	Animals were randomly assigned to groups using body weight as a blocking variable in the XYBION PATH/TOX system. Animals were randomly assigned to groups using body weight as a blocking variable in the XYBION PATH/TOX system.
	Metric 3: Observational Bias / Blinding Changes	High	Histopathology included an unblinded initial review and a blinded secondary review performed by an independent pathology quality assessment laboratory.
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	High	An appropriate vehicle control was used, and additional historical controls were used to evaluate the effects for certain neoplastic lesions. The study measured and controlled for relevant confounding factors, and confounding bias is unlikely to be a problem in this study.
Domain 4: Selective Reporting and Attrition			
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Study Citation:	NTP, (1993). NTP Toxicology and Carcinogenesis Studies of 1,3-Butadiene (CAS No. 106-99-0) in B6C3F1 Mice (Inhalation Studies). National Toxicology Program Technical Report Series 434:1-389.		
Health Outcome(s) and Reported Health Effect(s):	Cancer/Carcinogenesis-Malignant lymphoma, histiocytic sarcoma, cardiac hemangio- sarcoma; harderian gland adenoma, hepatocellular adenoma and carcinoma, alveolarbronchiolar adenoma and carcinoma; mammary gland carcinoma, adenocanthoma, and malignant mixed tumor, benign and malignant ovarian granulosa cell tumor; and forestomach squamous cell papilloma and carcinoma, intestinal carcinomas, renal tubule adenomas, skin sarcomas, Zymbal's gland adenomas and carcinomas, lymphocytic lymphomas-Immune/Hematological-Histopathology: bone marrow, thymus, lymph nodes, spleen. Erythrocyte counts, hemoglobin concentration, packed red cell volume, mean erythrocyte volume, Organ weight: spleen and thymus-Reproductive/Developmental-Histopathology: testis, ovaries, uterus, mammary gland, seminal vesicle, epididymides, prostate gland, Organ weight: right testis-Gastrointestinal-Histopathology: stomach, small intestine, large intestine, gallbladder, salivary gland, esophagus-Lung/Respiratory-Histopathology: trachea, larynx, lung, pharynx, nose, Organ weight: lungs-Neurological/Behavioral-Histopathology: Brain, Organ weight: brain-Renal/Kidney-Histopathology: kidney. Creatine kinase in serum. Organ weight: right kidney-Hepatic/Liver-Histopathology: liver. Lactate dehydrogenase in serum, Organ weight: liver-Cardiovascular-Histopathology: Heart, Organ weight: heart-Musculoskeletal-Histopathology: sternebrae-Other (please specify below) (Endocrine)-Histopathology: Thyroid, parathyroid gland, pancreas, adrenal gland-Ocular/Sensory-Histopathology: Harderian gland Inhalation-Vapor-Duration: Chronic (>90 days)-5-6-52-week(s)-Inhalation-Vapor-Duration: Subchronic (>30-90 days)-5-6-13-week(s)		
Duration and Exposure Route:			
Species:	Mouse-B6C3F1 - [mouse]-Male		
Chemical:	1,3-Butadiene- Parent compound		
HERO ID:	1419645		

Domain	Metric	Rating	Comments
	Metric 5: Selective Reporting and Attrition	Medium	The authors report 1 accidental death and many natural deaths and exposure-related deaths over the course of the study. The natural deaths were unrelated to the exposure and are unlikely to significantly bias the results of the study. All outcomes described in the methods were reported in the results.

Domain 5: Exposure Methods Sensitivity

Metric 6: Chemical administration and characterization	Medium	The authors performed independent analytical verification of the test substance identity and purity and monitored exposure chamber concentrations during the exposure. Exposure characterization was redone every 3 months and the authors reported <5% variability in chamber concentrations. There are no concerns regarding the exposure chamber used. Test substance storage conditions were not described, but the authors state that 7 different lots of the chemical were used over the 2-year exposure period, which may have mitigated the potential effects of chemical instability over the course of the experiment.
Metric 7: Exposure timing, frequency, and duration	High	The exposure duration and frequency are sensitive to detect the endpoints of interest and does include the critical window of sensitivity for detecting health effects from chronic-duration exposures.

Domain 6: Outcome Measures and Results Display

Metric 8: Endpoint sensitivity and specificity	Low	The species is appropriate and there are no concerns regarding the specificity or sensitivity of the outcome assessment protocols. 50 animals were used for the main study groups, which is informative for detecting the endpoints of interest at chronic durations. The different exposure concentrations in this study were assessed at different times in order to test the hypothesis that effects would be directly related to the product of the exposure concentration times the duration of exposure. While this hypothesis has scientific merit, the inconsistency between exposure durations at different doses makes this experiment difficult to interpret for the sake of evaluating dose-response.
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Study Citation:	NTP, (1993). NTP Toxicology and Carcinogenesis Studies of 1,3-Butadiene (CAS No. 106-99-0) in B6C3F1 Mice (Inhalation Studies). National Toxicology Program Technical Report Series 434:1-389.
Health Outcome(s) and Reported Health Effect(s):	Cancer/Carcinogenesis-Malignant lymphoma, histiocytic sarcoma, cardiac hemangio- sarcoma; harderian gland adenoma, hepatocellular adenoma and carcinoma, alveolarbronchiolar adenoma and carcinoma; mammary gland carcinoma, adenoacanthoma, and malignant mixed tumor, benign and malignant ovarian granulosa cell tumor; and forestomach squamous cell papilloma and carcinoma, intestinal carcinomas, renal tubule adenomas, skin sarcomas, Zymbal's gland adenomas and carcinomas, lymphocytic lymphomas-Immune/Hematological-Histopathology: bone marrow, thymus, lymph nodes, spleen. Erythrocyte counts, hemoglobin concentration, packed red cell volume, mean erythrocyte volume, Organ weight: spleen and thymus-Reproductive/Developmental-Histopathology: testis, ovaries, uterus, mammary gland, seminal vesicle, epididymides, prostate gland, Organ weight: right testis-Gastrointestinal-Histopathology: stomach, small intestine, large intestine, gallbladder, salivary gland, esophagus-Lung/Respiratory-Histopathology: trachea, larynx, lung, pharynx, nose, Organ weight: lungs-Neurological/Behavioral-Histopathology: Brain, Organ weight: brain-Renal/Kidney-Histopathology: kidney. Creatine kinase in serum. Organ weight: right kidney-Hepatic/Liver-Histopathology: liver. Lactate dehydrogenase in serum, Organ weight: liver-Cardiovascular-Histopathology: Heart, Organ weight: heart-Musculoskeletal-Histopathology: sternebrae-Other (please specify below) (Endocrine)-Histopathology: Thyroid, parathyroid gland, pancreas, adrenal gland-Ocular/Sensory-Histopathology: Harderian gland Inhalation-Vapor-Duration: Chronic (>90 days)-5-6-52-week(s)-Inhalation-Vapor-Duration: Subchronic (>30-90 days)-5-6-13-week(s)
Duration and Exposure Route:	
Species:	Mouse-B6C3F1 - [mouse]-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	1419645

Domain	Metric	Rating	Comments
Metric 9:	Results presentation	High	The results presentation generally includes full quantitative presentation in figures and tables and qualitative descriptions in the text. Incidence for neoplastic and nonneoplastic lesions are reported and the statistical methods employed by the study authors are appropriate.

Overall Quality Determination**Medium**

Study Citation:	Thurmond, L. M., Lauer, L. D., House, R. V., Stillman, W. S., Irons, R. D., Steinhagen, W. H., Dean, J. H. (1986). Effects of short-term inhalation exposure to 1,3-butadiene on murine immune functions. <i>Toxicology and Applied Pharmacology</i> 86(2):170-179.
Health Outcome(s) and Reported Health Effect(s):	Immune/Hematological-Organ weights (spleen and thymus); histopathology (spleen and thymus); functional immune assays (humoral immunity: antibody plaque-forming cell (PFC) response, cell-mediated immunity: mitogen-stimulated alloantigens lymphocyte proliferation assay and mixed lymphocyte cultures); Mechanistic (non-apical) endpoints (cellularities of spleen and bone marrow; analysis of splenocyte surface markers; immunolabeling of splenocytes; lymphocyte proliferation and cytotoxicity to alloantigens; spontaneous natural killer cell cytotoxicity).
Duration and Exposure Route:	Inhalation-Gas-Duration: Subchronic (>30-90 days)-5-6-12-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	62366

Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	Medium	All critical and most important information were reported. B6C3F1 mice (sex and source, age, initial body weights provided) were exposed whole-body to 1,3-butadiene (source, purity, composition reported). Details of caging, the inhalation chamber, and the number of animals per group (reported in results), were described. Animal husbandry (food and water availability, light cycle, and animals per cage) details were reported. Outcome assessment methods and results for all outcomes were reported. Missing information included: mouse age and initial body weights; temperature, humidity, and details of atmosphere generation.
Domain 2: Selection and Performance			
	Metric 2: Allocation	Low	The method of animal allocation into groups was not specified. The study did not specify whether animals were normalized to body weights.
	Metric 3: Observational Bias / Blinding Changes	Medium	Blinding was not specified; however, the potential for bias was mitigated because the endpoints were not considered to be subjective in nature.
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	Medium	A concurrent negative control group was exposed to filtered air only. The control responses were appropriate. There are no specific guidelines available for most of the immunotoxicity endpoints tested. It is unclear whether a positive control would have been reasonable, particularly in cases with no observed effects. Initial body weights and some animal husbandry conditions were not reported (e.g., temperature, humidity) and consistency among groups cannot be determined. Respiratory rates were not measured in an inhalation study. However, the test material is considered to be a respiratory irritant in humans, but not in animals.
Domain 4: Selective Reporting and Attrition			
	Metric 5: Selective Reporting and Attrition	Medium	The number of animals exposed per group per duration was not described in the methods, and results for only some of the endpoints specified the sample sizes. It is unclear whether all animals were accounted for in the results. Mortality was not reported in subchronic and chronic duration studies but none is assumed. The methods do not clearly indicate when some endpoints were measured (e.g., organ weights), and these results were reported for the 6-week exposure duration only.

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Study Citation:	Thurmond, L. M., Lauer, L. D., House, R. V., Stillman, W. S., Irons, R. D., Steinhagen, W. H., Dean, J. H. (1986). Effects of short-term inhalation exposure to 1,3-butadiene on murine immune functions. <i>Toxicology and Applied Pharmacology</i> 86(2):170-179.
Health Outcome(s) and Reported Health Effect(s):	Immune/Hematological-Organ weights (spleen and thymus); histopathology (spleen and thymus); functional immune assays (humoral immunity: antibody plaque-forming cell (PFC) response, cell-mediated immunity: mitogen-stimulated alloantigens lymphocyte proliferation assay and mixed lymphocyte cultures); Mechanistic (non-apical) endpoints (cellularities of spleen and bone marrow; analysis of splenocyte surface markers; immunolabeling of splenocytes; lymphocyte proliferation and cytotoxicity to alloantigens; spontaneous natural killer cell cytotoxicity).
Duration and Exposure Route:	Inhalation-Gas-Duration: Subchronic (>30-90 days)-5-6-12-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	62366

Domain	Metric	Rating	Comments
Domain 5: Exposure Methods Sensitivity			
	Metric 6: Chemical administration and characterization	Low	1,3-butadiene was procured from Exxon Corp in several intervals/batches. The purity of all batches was monitored using GC and was >99.5%. The concentration of dimer 4-vinyl-1-cyclohexane was ≤165 ppm. Dimer concentrations in the chambers were < 0.21 ppm. Atmosphere generation methods, including the equipment used, were not described. Animals were exposed whole-body in a dynamic chamber; the number of air changes per hour and the number of animals in each chamber were not specified. Concentrations in the chambers were monitored continuously with an infrared spectrophotometer. The reported concentration is presumed to be the target. No analytical values were provided, and it was not specified if the measured values were close to target or nominal concentrations. The authors justified the concentration tested, which was intended to mimic human occupational exposure. 1,250 ppm was reported as the short-term threshold limit value for human exposure.
	Metric 7: Exposure timing, frequency, and duration	High	The study used three durations: 6 weeks, 12 weeks and 24 weeks. The study introduction indicated that previous studies showed the appearance of murine thymic lymphomas following 20 weeks of exposure. This study aimed to identify functional immune system changes that may occur at earlier time points. Therefore, the three durations tested were appropriate for the purposes of the study. Additionally, animals were exposed 6hrs/day, 5 days/week which is typical for subchronic/chronic inhalation toxicity studies.

Domain	Metric	Rating	Comments
Domain 6: Outcome Measures and Results Display			
	Metric 8: Endpoint sensitivity and specificity	Low	This study evaluated a limited, but focused number of endpoints which spanned both <i>in vivo</i> and downstream <i>in vitro</i> evaluations of changes to immune-related organs and functional immune responses. The protocols for each test were generally described, with citations provided for further information for most. The tests were sensitive for the outcomes of interest although limitations for some tests were described (e.g., it was noted that there are no reliable cell surface markers for enumerating erythroid cell populations, and mitogen responses may have been fewer due to the use of unpurified splenocytes). The test animal species was appropriate and justified, but only males were used without further justification. The single exposure group was appropriate for this study, which tested three different durations. The study did not adequately describe or report group or sample sizes. Sample sizes were noted in Tables 1 and 2, but the number of animals used to generate data for Tables 3 and 4, or Figure 12 was not specified. Sufficient methodological details were not provided to determine consistency across groups.

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Study Citation:	Thurmond, L. M., Lauer, L. D., House, R. V., Stillman, W. S., Irons, R. D., Steinhagen, W. H., Dean, J. H. (1986). Effects of short-term inhalation exposure to 1,3-butadiene on murine immune functions. <i>Toxicology and Applied Pharmacology</i> 86(2):170-179.
Health Outcome(s) and Reported Health Effect(s):	Immune/Hematological-Organ weights (spleen and thymus); histopathology (spleen and thymus); functional immune assays (humoral immunity: antibody plaque-forming cell (PFC) response, cell-mediated immunity: mitogen-stimulated alloantigens lymphocyte proliferation assay and mixed lymphocyte cultures); Mechanistic (non-apical) endpoints (cellularities of spleen and bone marrow; analysis of splenocyte surface markers; immunolabeling of splenocytes; lymphocyte proliferation and cytotoxicity to alloantigens; spontaneous natural killer cell cytotoxicity).
Duration and Exposure Route:	Inhalation-Gas-Duration: Subchronic (>30-90 days)-5-6-12-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	62366

Domain	Metric	Rating	Comments
Metric 9:	Results presentation	Low	The statistical method (Dunnett's modification of Student's T test for multiple comparisons) was reported. Since the methods did not adequately specify which endpoints were measured at each duration, it is difficult to determine whether the results reported were adequate (e.g., organ weight data are only provided for the 6-week duration, but not the 12, or 12-week exposure durations; surface marker data were also only reported for 6-week exposure groups, but lymphocyte proliferation was reported for both 6 and 12-week exposure groups). Of the results shown, quantitative data for most endpoints are presented as means \pm SE (n = not reported in some cases).

Overall Quality Determination**Low**

Study Citation:	Thurmond, L. M., Lauer, L. D., House, R. V., Stillman, W. S., Irons, R. D., Steinhagen, W. H., Dean, J. H. (1986). Effects of short-term inhalation exposure to 1,3-butadiene on murine immune functions. <i>Toxicology and Applied Pharmacology</i> 86(2):170-179.
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Body weights
Duration and Exposure Route:	Inhalation-Gas-Duration: Subchronic (>30-90 days)-5-6-12-week(s)-Inhalation-Gas-Duration: Chronic (>90 days)-5-6-24-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	62366

Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	Medium	All critical and most important information were reported. B6C3F1 mice (sex and source, age, initial body weights provided) were exposed whole-body to 1,3-butadiene (source, purity, composition reported). Details of caging, the inhalation chamber, and the number of animals per group (reported in results), were described. Animal husbandry (food and water availability, light cycle, and animals per cage) details were reported. Outcome assessment methods and results for all outcomes were reported. Missing information included: mouse age and initial body weights; temperature, humidity, and details of atmosphere generation.
Domain 2: Selection and Performance			
	Metric 2: Allocation	Low	The method of animal allocation into groups was not specified. The study did not specify whether animals were normalized to body weights.
	Metric 3: Observational Bias / Blinding Changes	Medium	Blinding was not specified; however, the potential for bias was mitigated because the endpoints were not considered to be subjective in nature.
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	Medium	A concurrent negative control group was exposed to filtered air only. The control responses were appropriate. Initial body weights and some animal husbandry conditions were not reported (e.g., temperature, humidity) and consistency among groups cannot be determined. Respiratory rates were not measured in an inhalation study. However, the test material is considered to be a respiratory irritant in humans, but not in animals.
Domain 4: Selective Reporting and Attrition			
	Metric 5: Selective Reporting and Attrition	Low	The number of animals exposed per group per duration was not described in the methods. The results table specifies the sample size to be 5-6 rats, but it is unclear whether all animals were accounted for in the results. Mortality was not assessed/ reported in subchronic and chronic duration studies. The methods do not clearly indicate when some endpoints were measured (e.g., the methods indicate that body weights were weighed, but not whether body weights were weighed in animals from all three exposure durations); data for longer durations were not reported. It is unclear whether any animal attrition occurred.
Domain 5: Exposure Methods Sensitivity			

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Study Citation:	Thurmond, L. M., Lauer, L. D., House, R. V., Stillman, W. S., Irons, R. D., Steinhagen, W. H., Dean, J. H. (1986). Effects of short-term inhalation exposure to 1,3-butadiene on murine immune functions. <i>Toxicology and Applied Pharmacology</i> 86(2):170-179.
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Body weights
Duration and Exposure Route:	Inhalation-Gas-Duration: Subchronic (>30-90 days)-5-6-12-week(s)-Inhalation-Gas-Duration: Chronic (>90 days)-5-6-24-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	62366

Domain	Metric	Rating	Comments
Metric 6:	Chemical administration and characterization	Low	1,3-butadiene was procured from Exxon Corp in several intervals/batches. The purity of all batches was monitored using GC and was >99.5%. The concentration of dimer 4-vinyl-1-cyclohexane was ≤165 ppm. Dimer concentrations in the chambers were < 0.21 ppm. Atmosphere generation methods, including the equipment used, were not described. Animals were exposed whole-body in a dynamic chamber; the number of air changes per hour and the number of animals in each chamber were not specified. Concentrations in the chambers were monitored continuously with an infrared spectrophotometer. The reported concentration is presumed to be the target. No analytical values were provided, and it was not specified if the measured values were close to target or nominal concentrations. The authors justified the concentration tested, which was intended to mimic human occupational exposure. 1,250 ppm was reported as the short-term threshold limit value for human exposure.
Metric 7:	Exposure timing, frequency, and duration	High	The study used three durations: 6 weeks, 12 weeks and 24 weeks. The study introduction indicated that previous studies showed the appearance of murine thymic lymphomas following 20 weeks of exposure. This study aimed to identify functional immune system changes that may occur at earlier time points. Therefore, the three durations tested were appropriate for the purposes of the study and also for this outcome of interest. Additionally, animals were exposed 6hrs/day, 5 days/week which is typical for subchronic/chronic inhalation toxicity studies.

Domain 6: Outcome Measures and Results Display

Metric 8:	Endpoint sensitivity and specificity	Low	Body weights were only purportedly measured once at the time of sacrifice, which is atypical for subchronic/chronic duration studies, and the timing is not sensitive enough to assess potential changes throughout the exposure periods. The methods also do not specify whether body weights were measured in animals from all exposure-duration groups. The test animal species was appropriate and justified, but only males were used without further justification. The single exposure group was appropriate for this study, which tested three different durations. Sample sizes were noted in Table 1 which reports body weight data for the 6-week duration groups.
Metric 9:	Results presentation	Medium	The statistical method (Dunnett's modification of Student's T test for multiple comparisons) was reported. Since the methods did not adequately specify which endpoints were measured at each duration, it is difficult to determine whether the results reported were adequate (e.g., if results for body weight measurements of animals exposed for 12 or 24 weeks were missing). Of the results shown, the data were quantitatively reported as means ± SE.

Overall Quality Determination

Low

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Study Citation:	Thurmond, L. M., Lauer, L. D., House, R. V., Stillman, W. S., Irons, R. D., Steinhagen, W. H., Dean, J. H. (1986). Effects of short-term inhalation exposure to 1,3-butadiene on murine immune functions. <i>Toxicology and Applied Pharmacology</i> 86(2):170-179.
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Body weights
Duration and Exposure Route:	Inhalation-Gas-Duration: Subchronic (>30-90 days)-5-6-12-week(s)-Inhalation-Gas-Duration: Chronic (>90 days)-5-6-24-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	62366

Domain	Metric	Rating	Comments

Study Citation:	National Institutes of Health, Services, D.o. (1984). Toxicology and carcinogenesis studies of 1,3-butadiene (CAS no. 106-99-0) in B6C3F1 mice (inhalation studies). 288:1-111.
Health Outcome(s) and Reported Health Effect(s):	Mortality-Survival/mortality-Skin/Connective Tissue-Necropsy and histopathology of skin and gross lesions-Immune/Hematological-Necropsy and histopathology of mandibular lymph node, mesenteric lymph node, spleen, thymus, and gross lesions-Reproductive/Developmental-Necropsy and histopathology of mammary gland, seminal vesicles, prostate, testes, ovaries, uterus, and gross lesions-Musculoskeletal-Necropsy and histopathology of thigh muscle, sternebrae, vertebrae, femur (including bone marrow), costochondral junction (rib), and gross lesions-Gastrointestinal-Necropsy and histopathology of salivary gland, esophagus, stomach, gallbladder, duodenum, jejunum, ileum, colon, cecum, rectum, and gross lesions-Neurological/Behavioral-Necropsy and histopathology of sciatic nerve, brain, spinal cord, and gross lesions-Ocular/Sensory-Necropsy and histopathology of eyes and gross lesions-Lung/Respiratory-Necropsy and histopathology of nasal cavity, nasal turbinates, larynx, pharynx, trachea, lungs, bronchi, and gross lesions-Thyroid-Necropsy and histopathology of thyroid glands, parathyroids, and gross lesions-Other (please specify below) (Endocrine)-Necropsy and histopathology of pituitary gland, adrenal glands, pancreas, and gross lesions-Hepatic/Liver-Necropsy and histopathology of liver and gross lesions-Renal/Kidney-Necropsy and histopathology of kidneys, urinary bladder, and gross lesions-Cardiovascular-Necropsy and histopathology of heart and gross lesions-Other (please specify below) (Clinical signs)-Clinical signs, moribundity
Duration and Exposure Route:	Inhalation-Vapor-Duration: Short-term (>1-30 days)-5-6-2-week(s)-Inhalation-Vapor-Duration: Chronic (>90 days)-5-6-14-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	62372

Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	Medium	All critical information is reported. Some important information is not reported, including some animal husbandry conditions (including temperature and humidity) and parity of the animals; however, animals were only 4-5 weeks at the start of the study (~5 weeks for 2-week study; ~4-5 weeks for 14-week study). The test animal species, test article identity, concentrations tested and duration of exposure, route, quantitative or qualitative results for all endpoints examined, animal source, strain, age, sex, starting body weight, animal husbandry conditions (light/dark cycle), number of animals per cage, availability of food and water, test substance source, purity, method of administration, frequency of exposure, number of animals per group, and procedures used to measure endpoints were reported.
Domain 2: Selection and Performance			
	Metric 2: Allocation	High	The allocation method for assignment of animals to groups was based on random assignment (assignment based on a table of random numbers).
	Metric 3: Observational Bias / Blinding Changes	Medium	Measures to reduce observational bias were not reported and some of the endpoints were subjective (e.g., moribundity).
Domain 3: Confounding / Variable Control			

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Study Citation:	National Institutes of Health, Services, D.o. (1984). Toxicology and carcinogenesis studies of 1,3-butadiene (CAS no. 106-99-0) in B6C3F1 mice (inhalation studies). 288:1-111.
Health Outcome(s) and Reported Health Effect(s):	Mortality-Survival/mortality-Skin/Connective Tissue-Necropsy and histopathology of skin and gross lesions-Immune/Hematological-Necropsy and histopathology of mandibular lymph node, mesenteric lymph node, spleen, thymus, and gross lesions-Reproductive/Developmental-Necropsy and histopathology of mammary gland, seminal vesicles, prostate, testes, ovaries, uterus, and gross lesions-Musculoskeletal-Necropsy and histopathology of thigh muscle, sternebrae, vertebrae, femur (including bone marrow), costochondral junction (rib), and gross lesions-Gastrointestinal-Necropsy and histopathology of salivary gland, esophagus, stomach, gallbladder, duodenum, jejunum, ileum, colon, cecum, rectum, and gross lesions-Neurological/Behavioral-Necropsy and histopathology of sciatic nerve, brain, spinal cord, and gross lesions-Ocular/Sensory-Necropsy and histopathology of eyes and gross lesions-Lung/Respiratory-Necropsy and histopathology of nasal cavity, nasal turbinates, larynx, pharynx, trachea, lungs, bronchi, and gross lesions-Thyroid-Necropsy and histopathology of thyroid glands, parathyroids, and gross lesions-Other (please specify below) (Endocrine)-Necropsy and histopathology of pituitary gland, adrenal glands, pancreas, and gross lesions-Hepatic/Liver-Necropsy and histopathology of liver and gross lesions-Renal/Kidney-Necropsy and histopathology of kidneys, urinary bladder, and gross lesions-Cardiovascular-Necropsy and histopathology of heart and gross lesions-Other (please specify below) (Clinical signs)-Clinical signs, moribundity
Duration and Exposure Route:	Inhalation-Vapor-Duration: Short-term (>1-30 days)-5-6-2-week(s)-Inhalation-Vapor-Duration: Chronic (>90 days)-5-6-14-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	62372

Domain	Metric	Rating	Comments
Metric 4: Confounding / Variable Control	Low	There is some concern that confounding factors that may modify the results were uncontrolled due to incomplete reporting of animal husbandry (e.g., temperature, humidity, air changes). The study included an appropriate negative control. The control responses were appropriate for the outcomes reported. Animals were housed in stainless steel mesh cages. Contaminant levels in feed were measured; measurement of contaminants in bedding and water was not reported. Test substance purity was reported as 98.94 to 100%; small amounts of impurities were detected in the test substance, including methane and an unidentified substance.	
Domain 4: Selective Reporting and Attrition			
Metric 5: Selective Reporting and Attrition	High	All animals are accounted for in the presented results and there were no unexplained omissions or attrition. Quantitative or qualitative results were reported for all prespecified outcomes.	
Domain 5: Exposure Methods Sensitivity			
Metric 6: Chemical administration and characterization	Low	Some details of exposure administration were incompletely reported (e.g., whether whole-body or nose-only exposures). Purity was determined in a separate test. The test substance supplier was specified. Some details on timing (e.g., if animals were exposed at the same time of day to the extent possible) were incompletely reported. Additionally, test substance concentrations were not analytically determined.	
Metric 7: Exposure timing, frequency, and duration	High	The timing, duration, and frequency of the exposure appear to be appropriate for the study type and the outcomes/endpoints evaluated.	
Domain 6: Outcome Measures and Results Display			
Metric 8: Endpoint sensitivity and specificity	High	The procedures were sensitive and specific for the outcomes and endpoints of interest. The timing of the assessment of endpoints was appropriate.	

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Study Citation:	National Institutes of Health, Services, D.O. (1984). Toxicology and carcinogenesis studies of 1,3-butadiene (CAS no. 106-99-0) in B6C3F1 mice (inhalation studies). 288:1-111.
Health Outcome(s) and Reported Health Effect(s):	Mortality-Survival/mortality-Skin/Connective Tissue-Necropsy and histopathology of skin and gross lesions-Immune/Hematological-Necropsy and histopathology of mandibular lymph node, mesenteric lymph node, spleen, thymus, and gross lesions-Reproductive/Developmental-Necropsy and histopathology of mammary gland, seminal vesicles, prostate, testes, ovaries, uterus, and gross lesions-Musculoskeletal-Necropsy and histopathology of thigh muscle, sternebrae, vertebrae, femur (including bone marrow), costochondral junction (rib), and gross lesions-Gastrointestinal-Necropsy and histopathology of salivary gland, esophagus, stomach, gallbladder, duodenum, jejunum, ileum, colon, cecum, rectum, and gross lesions-Neurological/Behavioral-Necropsy and histopathology of sciatic nerve, brain, spinal cord, and gross lesions-Ocular/Sensory-Necropsy and histopathology of eyes and gross lesions-Lung/Respiratory-Necropsy and histopathology of nasal cavity, nasal turbinates, larynx, pharynx, trachea, lungs, bronchi, and gross lesions-Thyroid-Necropsy and histopathology of thyroid glands, parathyroids, and gross lesions-Other (please specify below) (Endocrine)-Necropsy and histopathology of pituitary gland, adrenal glands, pancreas, and gross lesions-Hepatic/Liver-Necropsy and histopathology of liver and gross lesions-Renal/Kidney-Necropsy and histopathology of kidneys, urinary bladder, and gross lesions-Cardiovascular-Necropsy and histopathology of heart and gross lesions-Other (please specify below) (Clinical signs)-Clinical signs, moribundity
Duration and Exposure Route:	Inhalation-Vapor-Duration: Short-term (>1-30 days)-5-6-2-week(s)-Inhalation-Vapor-Duration: Chronic (>90 days)-5-6-14-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	62372

Domain	Metric	Rating	Comments
	Metric 9: Results presentation	Uninformative	Some details of the results presentation were missing (e.g., individual animal data). Mean values are provided with variance (+/-SEM) for body weight data. Necropsy results are reported qualitatively (no compound-related effects). However, individual data were not presented for body weights. According to the NTP report (HERO ID 62372, p. 10), the 14-week studies were performed from May to Sept 1977 by Industrial Bio-test Laboratories. According to Table 1, the 2-week study was conducted by the same laboratory. It is presumed this was performed during the same timeframe. EPA considers the reporting of data in studies conducted by Industrial Bio-Test (IBT) laboratories during 1960-1978 to be unacceptable due to concerns about the integrity of the lab (i.e., discrepancies between raw data and study report, and gross deficiencies in study conduct were identified during an inspection by the FDA in 1976 and a follow-up audit by EPA and in collaboration with the Canadian Health and Welfare Department). Therefore, this metric and the data from these assays is uninformative.

Overall Quality Determination**Uninformative**

Study Citation:	National Institutes of Health,, Services,, D.o. (1984). Toxicology and carcinogenesis studies of 1,3-butadiene (CAS no. 106-99-0) in B6C3F1 mice (inhalation studies). 288:1-111.
Health Outcome(s) and Reported Health Effect(s):	Mortality-Survival/mortality-Nutritional/Metabolic-Body weight, body weight gain-Skin/Connective Tissue-Necropsy and histopathology of skin and gross lesions-Immune/Hematological-Necropsy and histopathology of mandibular lymph node, mesenteric lymph node, spleen, thymus, and gross lesions-Reproductive/Developmental-Necropsy and histopathology of mammary gland, seminal vesicles, prostate, testes, ovaries, uterus, and gross lesions-Musculoskeletal-Necropsy and histopathology of thigh muscle, sternebrae, vertebrae, femur (including bone marrow), costochondral junction (rib), and gross lesions-Gastrointestinal-Necropsy and histopathology of salivary gland, esophagus, stomach, gallbladder, duodenum, jejunum, ileum, colon, cecum, rectum, and gross lesions-Neurological/Behavioral-Necropsy and histopathology of sciatic nerve, brain, spinal cord, and gross lesions-Ocular/Sensory-Necropsy and histopathology of eyes and gross lesions-Lung/Respiratory-Necropsy and histopathology of nasal cavity, nasal turbinates, larynx, pharynx, trachea, lungs, bronchi, and gross lesions-Thyroid-Necropsy and histopathology of thyroid glands, parathyroids, and gross lesions-Other (please specify below) (Endocrine)-Necropsy and histopathology of pituitary gland, adrenal glands, pancreas, and gross lesions-Hepatic/Liver-Necropsy and histopathology of liver and gross lesions-Renal/Kidney-Necropsy and histopathology of kidneys, urinary bladder, and gross lesions-Cardiovascular-Necropsy and histopathology of heart and gross lesions-Other (please specify below) (Clinical signs)-Clinical signs, moribundity-Cancer/Carcinogenesis-Neoplastic lesions in tissues examined histologically (gross lesions, mandibular lymph node, mammary gland, sternebrae including marrow, thymus, trachea, lungs, bronchi, heart, thyroid glands, parathyroids, esophagus, stomach, colon, small intestine, liver, gallbladder, pancreas, spleen, kidneys, adrenal glands, urinary bladder, prostate, testes, ovaries, uterus, nasal cavity, nasal turbinates, brain, pituitary, pharynx, eyes (if abnormal)
Duration and Exposure Route:	Inhalation-Vapor-Duration: Chronic (>90 days)-5-6-60-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	62372

Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	Medium	All critical information and most important information are reported. Animal parity was not reported. The test animal species, test article identity, concentrations tested and duration of exposure, route, quantitative or qualitative results for all endpoints examined, animal source, strain, age, sex, starting body weight, animal husbandry conditions (temperature, light/dark cycle, and humidity), number of animals per cage, availability of food and water, test substance source, purity, method of administration, frequency of exposure, number of animals per group, and procedures used to measure endpoints were reported.
Domain 2: Selection and Performance			
	Metric 2: Allocation	High	The allocation method for assignment of animals to groups was based on distribution to weight blocks, and then assignment to groups according to a table of random numbers. Note: A deficiency in the allocation method was identified by the study authors and this is considered in Metric 3.
	Metric 3: Observational Bias / Blinding Changes	Medium	Measures to reduce observational bias were not reported and some of the endpoints were subjective (e.g., clinical signs, moribundity).
Domain 3: Confounding / Variable Control			

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Study Citation:	National Institutes of Health,, Services,, D.o. (1984). Toxicology and carcinogenesis studies of 1,3-butadiene (CAS no. 106-99-0) in B6C3F1 mice (inhalation studies). 288:1-111.
Health Outcome(s) and Reported Health Effect(s):	Mortality-Survival/mortality-Nutritional/Metabolic-Body weight, body weight gain-Skin/Connective Tissue-Necropsy and histopathology of skin and gross lesions-Immune/Hematological-Necropsy and histopathology of mandibular lymph node, mesenteric lymph node, spleen, thymus, and gross lesions-Reproductive/Developmental-Necropsy and histopathology of mammary gland, seminal vesicles, prostate, testes, ovaries, uterus, and gross lesions-Musculoskeletal-Necropsy and histopathology of thigh muscle, sternebrae, vertebrae, femur (including bone marrow), costochondral junction (rib), and gross lesions-Gastrointestinal-Necropsy and histopathology of salivary gland, esophagus, stomach, gallbladder, duodenum, jejunum, ileum, colon, cecum, rectum, and gross lesions-Neurological/Behavioral-Necropsy and histopathology of sciatic nerve, brain, spinal cord, and gross lesions-Ocular/Sensory-Necropsy and histopathology of eyes and gross lesions-Lung/Respiratory-Necropsy and histopathology of nasal cavity, nasal turbinates, larynx, pharynx, trachea, lungs, bronchi, and gross lesions-Thyroid-Necropsy and histopathology of thyroid glands, parathyroids, and gross lesions-Other (please specify below) (Endocrine)-Necropsy and histopathology of pituitary gland, adrenal glands, pancreas, and gross lesions-Hepatic/Liver-Necropsy and histopathology of liver and gross lesions-Renal/Kidney-Necropsy and histopathology of kidneys, urinary bladder, and gross lesions-Cardiovascular-Necropsy and histopathology of heart and gross lesions-Other (please specify below) (Clinical signs)-Clinical signs, moribundity-Cancer/Carcinogenesis-Neoplastic lesions in tissues examined histologically (gross lesions, mandibular lymph node, mammary gland, sternebrae including marrow, thymus, trachea, lungs, bronchi, heart, thyroid glands, parathyroids, esophagus, stomach, colon, small intestine, liver, gallbladder, pancreas, spleen, kidneys, adrenal glands, urinary bladder, prostate, testes, ovaries, uterus, nasal cavity, nasal turbinates, brain, pituitary, pharynx, eyes (if abnormal)
Duration and Exposure Route:	Inhalation-Vapor-Duration: Chronic (>90 days)-5-6-60-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	62372

Domain	Metric	Rating	Comments
Metric 4:	Confounding / Variable Control	Low	There is some concern that confounding factors that may modify the results were uncontrolled due to incomplete reporting of some methodological details (e.g., measurement of contaminants in water and bedding). Animal husbandry conditions (e.g., temperature, humidity, light/dark cycle, air changes) were the same across groups. The study included an appropriate negative control. The control responses were appropriate for the outcomes reported. Animals were housed in stainless steel cages. Contaminant levels in feed were measured; measurement of contaminants in bedding and water was not reported. Animals were monitored for overall health by measurement of antibody titers for murine viruses. The study report (HERO ID 62372, p. 32) states that due to an apparent inadequate randomization, initial weights in dosed males and females were 9-11% higher than those of controls ($p < 0.01$ by Mann-Whitney U test) and these approximate relationships were observed throughout most of the study. Test substance purity was reported as 98.94 to 100%; small amounts of impurities were detected in the test substance, including methane and an unidentified substance. The study report (HERO ID 62372) notes that two additional chemicals, epoxybutane and ethylene oxide, were being tested in the same room during part of the study of 1,3-butadiene.

Domain 4: Selective Reporting and Attrition

Metric 5:	Selective Reporting and Attrition	High	All animals are accounted for in the presented results and there were no unexplained omissions or attrition. Quantitative or qualitative results were reported for all prespecified outcomes.
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Domain 5: Exposure Methods Sensitivity

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Study Citation: National Institutes of Health,, Services,, D.o. (1984). Toxicology and carcinogenesis studies of 1,3-butadiene (CAS no. 106-99-0) in B6C3F1 mice (inhalation studies). 288:1-111.

Health Outcome(s) and Reported Health Effect(s): Mortality-Survival/mortality-Nutritional/Metabolic-Body weight, body weight gain-Skin/Connective Tissue-Necropsy and histopathology of skin and gross lesions-Immune/Hematological-Necropsy and histopathology of mandibular lymph node, mesenteric lymph node, spleen, thymus, and gross lesions-Reproductive/Developmental-Necropsy and histopathology of mammary gland, seminal vesicles, prostate, testes, ovaries, uterus, and gross lesions-Musculoskeletal-Necropsy and histopathology of thigh muscle, sternebrae, vertebrae, femur (including bone marrow), costochondral junction (rib), and gross lesions-Gastrointestinal-Necropsy and histopathology of salivary gland, esophagus, stomach, gallbladder, duodenum, jejunum, ileum, colon, cecum, rectum, and gross lesions-Neurological/Behavioral-Necropsy and histopathology of sciatic nerve, brain, spinal cord, and gross lesions-Ocular/Sensory-Necropsy and histopathology of eyes and gross lesions-Lung/Respiratory-Necropsy and histopathology of nasal cavity, nasal turbinates, larynx, pharynx, trachea, lungs, bronchi, and gross lesions-Thyroid-Necropsy and histopathology of thyroid glands, parathyroids, and gross lesions-Other (please specify below) (Endocrine)-Necropsy and histopathology of pituitary gland, adrenal glands, pancreas, and gross lesions-Hepatic/Liver-Necropsy and histopathology of liver and gross lesions-Renal/Kidney-Necropsy and histopathology of kidneys, urinary bladder, and gross lesions-Cardiovascular-Necropsy and histopathology of heart and gross lesions-Other (please specify below) (Clinical signs)-Clinical signs, moribundity-Cancer/Carcinogenesis-Neoplastic lesions in tissues examined histologically (gross lesions, mandibular lymph node, mammary gland, sternebrae including marrow, thymus, trachea, lungs, bronchi, heart, thyroid glands, parathyroids, esophagus, stomach, colon, small intestine, liver, gallbladder, pancreas, spleen, kidneys, adrenal glands, urinary bladder, prostate, testes, ovaries, uterus, nasal cavity, nasal turbinates, brain, pituitary, pharynx, eyes (if abnormal)

Duration and Exposure Route: Inhalation-Vapor-Duration: Chronic (>90 days)-5-6-60-week(s)

Species: Mouse-B6C3F1 - [mouse]-Both
Chemical: 1,3-Butadiene- Parent compound
HERO ID: 62372

Domain	Metric	Rating	Comments
	Metric 6: Chemical administration and characterization	Medium	Some details of exposure administration were incompletely reported (e.g., whether whole-body or nose-only exposures). Purity was determined in a separate test. Test substance concentrations were analytically confirmed. Some details on timing (e.g., if animals were exposed at the same time of day to the extent possible) were incompletely reported. but this is expected to have minimal impact on the study results. Test concentrations were analytically verified.
	Metric 7: Exposure timing, frequency, and duration	High	The timing, duration, and frequency of the exposure appear to be appropriate for the study type and the outcomes/endpoints evaluated. Although the study was designed to evaluate tumors and the duration was only 61 weeks, tumors were observed in the study. Therefore, the shorter duration of exposure of this study relative to carcinogenicity assay guidelines (e.g., 2 years for rats, 18 months to 2 years for mice) is not considered a deficiency.

Domain 6: Outcome Measures and Results Display

Metric 8:	Endpoint sensitivity and specificity	High	The procedures were sensitive and specific for the outcomes and endpoints of interest. The timing of the assessment of endpoints was appropriate.
Metric 9:	Results presentation	High	The results presentation appears to be appropriate for the study type and endpoints that are evaluated. Mean values are provided with variance (+/-SEM) for body weight data. Individual data are reported for pathology/necropsy data.

Overall Quality Determination

High

Study Citation:	National Institutes of Health,, Services,, D.o. (1984). Toxicology and carcinogenesis studies of 1,3-butadiene (CAS no. 106-99-0) in B6C3F1 mice (inhalation studies). 288:1-111.
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Body weight, body weight gain-Neurological/Behavioral-Necropsy and histopathology of sciatic nerve, brain, spinal cord, and gross lesions
Duration and Exposure Route:	Inhalation-Vapor-Duration: Chronic (>90 days)-5-6-60-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	62372

Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	Medium	All critical information and most important information are reported. Animal parity was not reported. The test animal species, test article identity, concentrations tested and duration of exposure, route, quantitative or qualitative results for all endpoints examined, animal source, strain, age, sex, starting body weight, animal husbandry conditions (temperature, light/dark cycle, and humidity), number of animals per cage, availability of food and water, test substance source, purity, method of administration, frequency of exposure, number of animals per group, and procedures used to measure endpoints were reported.
Domain 2: Selection and Performance			
	Metric 2: Allocation	High	The allocation method for assignment of animals to groups was based on distribution to weight blocks, and then assignment to groups according to a table of random numbers. Note: A deficiency in the allocation method was identified by the study authors and this is considered in Metric 3.
	Metric 3: Observational Bias / Blinding Changes	Medium	Measures to reduce observational bias were not reported and some of the endpoints were subjective (e.g., clinical signs, moribundity).

Domain 3: Confounding / Variable Control

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Study Citation:	National Institutes of Health, Services, D.o. (1984). Toxicology and carcinogenesis studies of 1,3-butadiene (CAS no. 106-99-0) in B6C3F1 mice (inhalation studies). 288:1-111.		
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Body weight, body weight gain-Neurological/Behavioral-Necropsy and histopathology of sciatic nerve, brain, spinal cord, and gross lesions		
Duration and Exposure Route:	Inhalation-Vapor-Duration: Chronic (>90 days)-5-6-60-week(s)		
Species:	Mouse-B6C3F1 - [mouse]-Both		
Chemical:	1,3-Butadiene- Parent compound		
HERO ID:	62372		

Domain	Metric	Rating	Comments
	Metric 4: Confounding / Variable Control	Low	There is some concern that confounding factors that may modify the results were uncontrolled due to incomplete reporting of some methodological details (e.g., measurement of contaminants in water and bedding). Animal husbandry conditions (e.g., temperature, humidity, light/dark cycle, air changes) were the same across groups. The study included an appropriate negative control. The control responses were appropriate for the outcomes reported. Animals were housed in stainless steel cages. Contaminant levels in feed were measured; measurement of contaminants in bedding and water was not reported. Animals were monitored for overall health by measurement of antibody titers for murine viruses. The study report (HERO ID 62372, p. 32) states that due to an apparent inadequate randomization, initial weights in dosed males and females were 9-11% higher than those of controls ($p < 0.01$ by Mann-Whitney U test) and these approximate relationships were observed throughout most of the study. Test substance purity was reported as 98.94 to 100%; small amounts of impurities were detected in the test substance, including methane and an unidentified substance. The study report (HERO ID 62372) notes that two additional chemicals, epoxybutane and ethylene oxide, were being tested in the same room during part of the study of 1,3-butadiene. The study results for body weight are not reliable due to the large differences in starting weight between controls and dosed animals. Weight gain could still be calculated but would be less relevant with different starting weights.
Domain 4: Selective Reporting and Attrition			
	Metric 5: Selective Reporting and Attrition	High	All animals are accounted for in the presented results and there were no unexplained omissions or attrition. Quantitative or qualitative results were reported for all prespecified outcomes.
Domain 5: Exposure Methods Sensitivity			
	Metric 6: Chemical administration and characterization	Medium	Some details of exposure administration were incompletely reported (e.g., whether whole-body or nose-only exposures). Purity was determined in a separate test. Test substance concentrations were analytically confirmed. Some details on timing (e.g., if animals were exposed at the same time of day to the extent possible) were incompletely reported, but this is expected to have minimal impact on the study results. Test concentrations were analytically verified.

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Study Citation:	National Institutes of Health,, Services,, D.o. (1984). Toxicology and carcinogenesis studies of 1,3-butadiene (CAS no. 106-99-0) in B6C3F1 mice (inhalation studies). 288:1-111.		
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Body weight, body weight gain-Neurological/Behavioral-Necropsy and histopathology of sciatic nerve, brain, spinal cord, and gross lesions		
Duration and Exposure Route:	Inhalation-Vapor-Duration: Chronic (>90 days)-5-6-60-week(s)		
Species:	Mouse-B6C3F1 - [mouse]-Both		
Chemical:	1,3-Butadiene- Parent compound		
HERO ID:	62372		

Domain	Metric	Rating	Comments
Metric 7:	Exposure timing, frequency, and duration	High	The timing, duration, and frequency of the exposure appear to be appropriate for the study type and the outcomes/endpoints evaluated. Although the study was designed to evaluate tumors and the duration was only 61 weeks, tumors were observed in the study. Therefore, the shorter duration of exposure of this study relative to carcinogenicity assay guidelines (e.g., 2 years for rats, 18 months to 2 years for mice) is not considered a deficiency.

Domain 6: Outcome Measures and Results Display

Metric 8:	Endpoint sensitivity and specificity	High	The procedures were sensitive and specific for the outcomes and endpoints of interest. The timing of the assessment of endpoints was appropriate.
Metric 9:	Results presentation	High	The results presentation appears to be appropriate for the study type and endpoints that are evaluated. Mean values are provided with variance (+/-SEM) for body weight data. Individual data are reported for pathology/necropsy data.

Overall Quality Determination**Low**

Study Citation:	NTP, (1993). NTP Toxicology and Carcinogenesis Studies of 1,3-Butadiene (CAS No. 106-99-0) in B6C3F1 Mice (Inhalation Studies). National Toxicology Program Technical Report Series 434:1-389.		
Health Outcome(s) and Reported	Mortality-Survival-Nutritional/Metabolic-Body weights		
Health Effect(s):			
Duration and	Inhalation-Vapor-Duration: Chronic (>90 days)-5-6-103-week(s)		
Exposure Route:			
Species:	Mouse-B6C3F1 - [mouse]-Both		
Chemical:	1,3-Butadiene- Parent compound		
HERO ID:	1419645		

Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	High	Test substance identity, source and purity were reported, and the identity and purity were confirmed by infrared spectroscopy and gas chromatography. The inhalation chamber was described in detail. Test animal species, sex, strain, starting age and source were reported. Starting body weights are not reported in the methods but are presented in the results. Animal housing conditions that included number of animals per cage, food and water availability, temperature, humidity, day/night cycle, and room air changes per hour were reported. The study design is described in detail and endpoint assessment methods were reported.
Domain 2: Selection and Performance			
	Metric 2: Allocation	High	Animals were randomly assigned to groups using body weight as a blocking variable in the XYBION PATH/TOX system. Animals were randomly assigned to groups using body weight as a blocking variable in the XYBION PATH/TOX system.
	Metric 3: Observational Bias / Blinding Changes	Medium	No measures to reduce observational bias were described, but measured endpoints were objective in nature.
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	High	An appropriate vehicle control was used, and additional historical controls were used to evaluate the effects for certain neoplastic lesions. The study measured and controlled for relevant confounding factors, and confounding bias is unlikely to be a problem in this study.
Domain 4: Selective Reporting and Attrition			
	Metric 5: Selective Reporting and Attrition	Medium	The authors report 1 accidental death and many natural deaths and exposure-related deaths over the course of the study. The natural deaths were unrelated to the exposure and are unlikely to significantly bias the results of the study. All outcomes described in the methods were reported in the results.
Domain 5: Exposure Methods Sensitivity			
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Study Citation:	NTP, (1993). NTP Toxicology and Carcinogenesis Studies of 1,3-Butadiene (CAS No. 106-99-0) in B6C3F1 Mice (Inhalation Studies). National Toxicology Program Technical Report Series 434:1-389.		
Health Outcome(s) and Reported Health Effect(s):	Mortality-Survival-Nutritional/Metabolic-Body weights		
Duration and Exposure Route:	Inhalation-Vapor-Duration: Chronic (>90 days)-5-6-103-week(s)		
Species:	Mouse-B6C3F1 - [mouse]-Both		
Chemical:	1,3-Butadiene- Parent compound		
HERO ID:	1419645		

Domain	Metric	Rating	Comments
Metric 6:	Chemical administration and characterization	Medium	The authors performed independent analytical verification of the test substance identity and purity and monitored exposure chamber concentrations during the exposure. Exposure characterization was redone every 3 months and the authors reported <5% variability in chamber concentrations. There are no concerns regarding the exposure chamber used. Test substance storage conditions were not described, but the authors state that 7 different lots of the chemical were used over the 2-year exposure period, which may have mitigated the potential effects of chemical instability over the course of the experiment.
Metric 7:	Exposure timing, frequency, and duration	High	The exposure duration and frequency are sensitive to detect the endpoints of interest and does include the critical window of sensitivity for detecting health effects from chronic-duration exposures.

Domain 6: Outcome Measures and Results Display

Metric 8:	Endpoint sensitivity and specificity	Medium	The species is appropriate and there are no concerns regarding the specificity or sensitivity of the outcome assessment protocols. 70 animals were used for the main study groups, which is informative for detecting the endpoints of interest at chronic durations. Interim evaluations used only 10 animals per group at month 9 and 15, which are less informative for assessing chronic-duration exposures. The interim evaluations also only performed histopathology on the highest exposure group with a survival of at least 60%, meaning that some aspects of the results were not comprehensive.
Metric 9:	Results presentation	Medium	The results presentation generally includes full quantitative presentation in figures and tables and qualitative descriptions in the text. Notably, measures of variance for continuous endpoints are omitted from figures and tables, which may have a minor impact on the ability to interpret the results.

Overall Quality Determination**High**

Study Citation:	NTP, (1993). NTP Toxicology and Carcinogenesis Studies of 1,3-Butadiene (CAS No. 106-99-0) in B6C3F1 Mice (Inhalation Studies). National Toxicology Program Technical Report Series 434:1-389.		
Health Outcome(s) and Reported Health Effect(s):	Mortality-Survival-Nutritional/Metabolic-Body weights		
Duration and Exposure Route:	Inhalation-Vapor-Duration: Chronic (>90 days)-5-6-52-week(s)-Inhalation-Vapor-Duration: Subchronic (>30-90 days)-5-6-13-week(s)		
Species:	Mouse-B6C3F1 - [mouse]-Male		
Chemical:	1,3-Butadiene- Parent compound		
HERO ID:	1419645		

Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	High	Test substance identity, source and purity were reported, and the identity and purity were confirmed by infrared spectroscopy and gas chromatography. The inhalation chamber was described in detail. Test animal species, sex, strain, starting age and source were reported. Starting body weights are not reported in the methods but are presented in the results. Animal housing conditions that included number of animals per cage, food and water availability, temperature, humidity, day/night cycle, and room air changes per hour were reported. The study design is described in detail and endpoint assessment methods were reported.
Domain 2: Selection and Performance			
	Metric 2: Allocation	High	Animals were randomly assigned to groups using body weight as a blocking variable in the XYBION PATH/TOX system. Animals were randomly assigned to groups using body weight as a blocking variable in the XYBION PATH/TOX system.
	Metric 3: Observational Bias / Blinding Changes	Medium	No measures to reduce observational bias were described, but measured endpoints were objective in nature or included initial histopathology and were not subject to observational bias. Histopathology was performed by an independent pathology quality assessment laboratory, but it is not stated whether assessors did a secondary blinded review or only did initial histopathology.
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	High	An appropriate vehicle control was used, and additional historical controls were used to evaluate the effects for certain neoplastic lesions. The study measured and controlled for relevant confounding factors, and confounding bias is unlikely to be a problem in this study.
Domain 4: Selective Reporting and Attrition			
	Metric 5: Selective Reporting and Attrition	Medium	The authors report 1 accidental death and many natural deaths and exposure-related deaths over the course of the study. The natural deaths were unrelated to the exposure and are unlikely to significantly bias the results of the study. All outcomes described in the methods were reported in the results.
Domain 5: Exposure Methods Sensitivity			

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Study Citation:	NTP, (1993). NTP Toxicology and Carcinogenesis Studies of 1,3-Butadiene (CAS No. 106-99-0) in B6C3F1 Mice (Inhalation Studies). National Toxicology Program Technical Report Series 434:1-389.		
Health Outcome(s) and Reported Health Effect(s):	Mortality-Survival-Nutritional/Metabolic-Body weights		
Duration and Exposure Route:	Inhalation-Vapor-Duration: Chronic (>90 days)-5-6-52-week(s)-Inhalation-Vapor-Duration: Subchronic (>30-90 days)-5-6-13-week(s)		
Species:	Mouse-B6C3F1 - [mouse]-Male		
Chemical:	1,3-Butadiene- Parent compound		
HERO ID:	1419645		

Domain	Metric	Rating	Comments
	Metric 6: Chemical administration and characterization	Medium	The authors performed independent analytical verification of the test substance identity and purity and monitored exposure chamber concentrations during the exposure. Exposure characterization was redone every 3 months and the authors reported <5% variability in chamber concentrations. There are no concerns regarding the exposure chamber used. Test substance storage conditions were not described, but the authors state that 7 different lots of the chemical were used over the 2-year exposure period, which may have mitigated the potential effects of chemical instability over the course of the experiment.
	Metric 7: Exposure timing, frequency, and duration	High	The exposure duration and frequency are sensitive to detect the endpoints of interest and does include the critical window of sensitivity for detecting health effects from chronic-duration exposures.

Domain 6: Outcome Measures and Results Display

Metric 8: Endpoint sensitivity and specificity	Low	The species is appropriate and there are no concerns regarding the specificity or sensitivity of the outcome assessment protocols. 50 animals were used for the main study groups, which is informative for detecting the endpoints of interest at chronic durations. The different exposure concentrations in this study were assessed at different times in order to test the hypothesis that effects would be directly related to the product of the exposure concentration times the duration of exposure. While this hypothesis has scientific merit, the inconsistency between exposure durations at different doses makes this experiment difficult to interpret for the sake of evaluating dose-response.
Metric 9: Results presentation	Medium	The results presentation generally includes full quantitative presentation in figures and tables and qualitative descriptions in the text. Notably, measures of variance for continuous endpoints are omitted from figures and tables, which may have a minor impact on the ability to interpret the results.

Overall Quality Determination**Medium**

Study Citation:	NTP, (1993). NTP Toxicology and Carcinogenesis Studies of 1,3-Butadiene (CAS No. 106-99-0) in B6C3F1 Mice (Inhalation Studies). National Toxicology Program Technical Report Series 434:1-389.
Health Outcome(s) and Reported Health Effect(s):	Cancer/Carcinogenesis-Malignant lymphoma, histiocytic sarcoma, cardiac hemangio- sarcoma; harderian gland adenoma, hepatocellular adenoma and carcinoma, alveolarbronchiolar adenoma and carcinoma; mammary gland carcinoma, adenocanthoma, and malignant mixed tumor, benign and malignant ovarian granulosa cell tumor; and forestomach squamous cell papilloma and carcinoma, intestinal carcinomas, renal tubule adenomas, skin sarcomas, Zymbal's gland adenomas and carcinomas, lymphocytic lymphomas-Immune/Hematological-Histopathology: bone marrow, thymus, lymph nodes, spleen. Erythrocyte counts, hemoglobin concentration, packed red cell volume, mean erythrocyte volume, Organ weight: spleen and thymus-Reproductive/Developmental-Histopathology: testis, ovaries, uterus, mammary gland, seminal vesicle, epididymides, prostate gland, Organ weight: right testis-Gastrointestinal-Histopathology: stomach, small intestine, large intestine, gallbladder, salivary gland, esophagus-Lung/Respiratory-Histopathology: trachea, larynx, lung, pharynx, nose, Organ weight: lungs-Neurological/Behavioral-Histopathology: Brain, Organ weight: brain-Renal/Kidney-Histopathology: kidney. Creatine kinase in serum. Organ weight: right kidney-Hepatic/Liver-Histopathology: liver. Lactate dehydrogenase in serum, Organ weight: liver-Cardiovascular-Histopathology: Heart, Organ weight: heart-Musculoskeletal-Histopathology: sternebrae-Other (please specify below) (Endocrine)-Histopathology: Thyroid, parathyroid gland, pancreas, adrenal gland-Ocular/Sensory-Histopathology: Harderian gland
Duration and Exposure Route:	Inhalation-Vapor-Duration: Chronic (>90 days)-5-6-103-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	1419645

Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	High	Test substance identity, source and purity were reported, and the identity and purity were confirmed by infrared spectroscopy and gas chromatography. The inhalation chamber was described in detail. Test animal species, sex, strain, starting age and source were reported. Starting body weights are not reported in the methods but are presented in the results. Animal housing conditions that included number of animals per cage, food and water availability, temperature, humidity, day/night cycle, and room air changes per hour were reported. The study design is described in detail and endpoint assessment methods were reported.
Domain 2: Selection and Performance			
	Metric 2: Allocation	High	Animals were randomly assigned to groups using body weight as a blocking variable in the XYBION PATH/TOX system. Animals were randomly assigned to groups using body weight as a blocking variable in the XYBION PATH/TOX system.
	Metric 3: Observational Bias / Blinding Changes	High	Histopathology included an unblinded initial review and a blinded secondary review performed by an independent pathology quality assessment laboratory.
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	High	An appropriate vehicle control was used, and additional historical controls were used to evaluate the effects for certain neoplastic lesions. The study measured and controlled for relevant confounding factors, and confounding bias is unlikely to be a problem in this study.
Domain 4: Selective Reporting and Attrition			
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Study Citation:	NTP, (1993). NTP Toxicology and Carcinogenesis Studies of 1,3-Butadiene (CAS No. 106-99-0) in B6C3F1 Mice (Inhalation Studies). National Toxicology Program Technical Report Series 434:1-389.
Health Outcome(s) and Reported Health Effect(s):	Cancer/Carcinogenesis-Malignant lymphoma, histiocytic sarcoma, cardiac hemangio- sarcoma; harderian gland adenoma, hepatocellular adenoma and carcinoma, alveolarbronchiolar adenoma and carcinoma; mammary gland carcinoma, adenocanthoma, and malignant mixed tumor, benign and malignant ovarian granulosa cell tumor; and forestomach squamous cell papilloma and carcinoma, intestinal carcinomas, renal tubule adenomas, skin sarcomas, Zymbal's gland adenomas and carcinomas, lymphocytic lymphomas-Immune/Hematological-Histopathology: bone marrow, thymus, lymph nodes, spleen. Erythrocyte counts, hemoglobin concentration, packed red cell volume, mean erythrocyte volume, Organ weight: spleen and thymus-Reproductive/Developmental-Histopathology: testis, ovaries, uterus, mammary gland, seminal vesicle, epididymides, prostate gland, Organ weight: right testis-Gastrointestinal-Histopathology: stomach, small intestine, large intestine, gallbladder, salivary gland, esophagus-Lung/Respiratory-Histopathology: trachea, larynx, lung, pharynx, nose, Organ weight: lungs-Neurological/Behavioral-Histopathology: Brain, Organ weight: brain-Renal/Kidney-Histopathology: kidney. Creatine kinase in serum. Organ weight: right kidney-Hepatic/Liver-Histopathology: liver. Lactate dehydrogenase in serum, Organ weight: liver-Cardiovascular-Histopathology: Heart, Organ weight: heart-Musculoskeletal-Histopathology: sternebrae-Other (please specify below) (Endocrine)-Histopathology: Thyroid, parathyroid gland, pancreas, adrenal gland-Ocular/Sensory-Histopathology: Harderian gland
Duration and Exposure Route:	Inhalation-Vapor-Duration: Chronic (>90 days)-5-6-103-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	1419645

Domain	Metric	Rating	Comments
Metric 5:	Selective Reporting and Attrition	Medium	The authors report 1 accidental death and many natural deaths and exposure-related deaths over the course of the study. The natural deaths were unrelated to the exposure and are unlikely to significantly bias the results of the study. All outcomes described in the methods were reported in the results.

Domain 5: Exposure Methods Sensitivity

Metric 6:	Chemical administration and characterization	Medium	The authors performed independent analytical verification of the test substance identity and purity and monitored exposure chamber concentrations during the exposure. Exposure characterization was redone every 3 months and the authors reported <5% variability in chamber concentrations. There are no concerns regarding the exposure chamber used. Test substance storage conditions were not described, but the authors state that 7 different lots of the chemical were used over the 2-year exposure period, which may have mitigated the potential effects of chemical instability over the course of the experiment.
Metric 7:	Exposure timing, frequency, and duration	High	The exposure duration and frequency are sensitive to detect the endpoints of interest and does include the critical window of sensitivity for detecting health effects from chronic-duration exposures.

Domain 6: Outcome Measures and Results Display

Metric 8:	Endpoint sensitivity and specificity	Medium	The species is appropriate and there are no concerns regarding the specificity or sensitivity of the outcome assessment protocols. 70 animals were used for the main study groups, which is informative for detecting the endpoints of interest at chronic durations. Interim evaluations used only 10 animals per group at month 9 and 15, which are less informative for assessing chronic-duration exposures. The interim evaluations also only performed histopathology on the highest exposure group with a survival of at least 60%, meaning that some aspects of the results were not comprehensive.
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Study Citation:	NTP, (1993). NTP Toxicology and Carcinogenesis Studies of 1,3-Butadiene (CAS No. 106-99-0) in B6C3F1 Mice (Inhalation Studies). National Toxicology Program Technical Report Series 434:1-389.
Health Outcome(s) and Reported Health Effect(s):	Cancer/Carcinogenesis-Malignant lymphoma, histiocytic sarcoma, cardiac hemangio- sarcoma; harderian gland adenoma, hepatocellular adenoma and carcinoma, alveolarbronchiolar adenoma and carcinoma; mammary gland carcinoma, adenocanthoma, and malignant mixed tumor, benign and malignant ovarian granulosa cell tumor; and forestomach squamous cell papilloma and carcinoma, intestinal carcinomas, renal tubule adenomas, skin sarcomas, Zymbal's gland adenomas and carcinomas, lymphocytic lymphomas-Immune/Hematological-Histopathology: bone marrow, thymus, lymph nodes, spleen. Erythrocyte counts, hemoglobin concentration, packed red cell volume, mean erythrocyte volume, Organ weight: spleen and thymus-Reproductive/Developmental-Histopathology: testis, ovaries, uterus, mammary gland, seminal vesicle, epididymides, prostate gland, Organ weight: right testis-Gastrointestinal-Histopathology: stomach, small intestine, large intestine, gallbladder, salivary gland, esophagus-Lung/Respiratory-Histopathology: trachea, larynx, lung, pharynx, nose, Organ weight: lungs-Neurological/Behavioral-Histopathology: Brain, Organ weight: brain-Renal/Kidney-Histopathology: kidney. Creatine kinase in serum. Organ weight: right kidney-Hepatic/Liver-Histopathology: liver. Lactate dehydrogenase in serum, Organ weight: liver-Cardiovascular-Histopathology: Heart, Organ weight: heart-Musculoskeletal-Histopathology: sternebrae-Other (please specify below) (Endocrine)-Histopathology: Thyroid, parathyroid gland, pancreas, adrenal gland-Ocular/Sensory-Histopathology: Harderian gland
Duration and Exposure Route:	Inhalation-Vapor-Duration: Chronic (>90 days)-5-6-103-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Both
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	1419645

Domain	Metric	Rating	Comments
Metric 9:	Results presentation	High	The results presentation generally includes full quantitative presentation in figures and tables and qualitative descriptions in the text. Incidence for neoplastic and nonneoplastic lesions are reported and the statistical methods employed by the study authors are appropriate.

Overall Quality Determination

High

Study Citation:	NTP, (1993). NTP Toxicology and Carcinogenesis Studies of 1,3-Butadiene (CAS No. 106-99-0) in B6C3F1 Mice (Inhalation Studies). National Toxicology Program Technical Report Series 434:1-389.
Health Outcome(s) and Reported Health Effect(s):	Cancer/Carcinogenesis-Malignant lymphoma, histiocytic sarcoma, cardiac hemangio- sarcoma; harderian gland adenoma, hepatocellular adenoma and carcinoma, alveolarbronchiolar adenoma and carcinoma; mammary gland carcinoma, adenoacanthoma, and malignant mixed tumor, benign and malignant ovarian granulosa cell tumor; and forestomach squamous cell papilloma and carcinoma, intestinal carcinomas, renal tubule adenomas, skin sarcomas, Zymbal's gland adenomas and carcinomas, lymphocytic lymphomas-Immune/Hematological-Histopathology: bone marrow, thymus, lymph nodes, spleen. Erythrocyte counts, hemoglobin concentration, packed red cell volume, mean erythrocyte volume, Organ weight: spleen and thymus-Reproductive/Developmental-Histopathology: testis, ovaries, uterus, mammary gland, seminal vesicle, epididymides, prostate gland, Organ weight: right testis-Gastrointestinal-Histopathology: stomach, small intestine, large intestine, gallbladder, salivary gland, esophagus-Lung/Respiratory-Histopathology: trachea, larynx, lung, pharynx, nose, Organ weight: lungs-Neurological/Behavioral-Histopathology: Brain, Organ weight: brain-Renal/Kidney-Histopathology: kidney. Creatine kinase in serum. Organ weight: right kidney-Hepatic/Liver-Histopathology: liver. Lactate dehydrogenase in serum, Organ weight: liver-Cardiovascular-Histopathology: Heart, Organ weight: heart-Musculoskeletal-Histopathology: sternebrae-Other (please specify below) (Endocrine)-Histopathology: Thyroid, parathyroid gland, pancreas, adrenal gland-Ocular/Sensory-Histopathology: Harderian gland Inhalation-Vapor-Duration: Chronic (>90 days)-5-6-52-week(s)-Inhalation-Vapor-Duration: Subchronic (>30-90 days)-5-6-13-week(s)
Duration and Exposure Route:	
Species:	Mouse-B6C3F1 - [mouse]-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	1419645

Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	High	Test substance identity, source and purity were reported, and the identity and purity were confirmed by infrared spectroscopy and gas chromatography. The inhalation chamber was described in detail. Test animal species, sex, strain, starting age and source were reported. Starting body weights are not reported in the methods but are presented in the results. Animal housing conditions that included number of animals per cage, food and water availability, temperature, humidity, day/night cycle, and room air changes per hour were reported. The study design is described in detail and endpoint assessment methods were reported.
Domain 2: Selection and Performance			
	Metric 2: Allocation	High	Animals were randomly assigned to groups using body weight as a blocking variable in the XYBION PATH/TOX system. Animals were randomly assigned to groups using body weight as a blocking variable in the XYBION PATH/TOX system.
	Metric 3: Observational Bias / Blinding Changes	High	Histopathology included an unblinded initial review and a blinded secondary review performed by an independent pathology quality assessment laboratory.
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	High	An appropriate vehicle control was used, and additional historical controls were used to evaluate the effects for certain neoplastic lesions. The study measured and controlled for relevant confounding factors, and confounding bias is unlikely to be a problem in this study.
Domain 4: Selective Reporting and Attrition			
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Study Citation:	NTP, (1993). NTP Toxicology and Carcinogenesis Studies of 1,3-Butadiene (CAS No. 106-99-0) in B6C3F1 Mice (Inhalation Studies). National Toxicology Program Technical Report Series 434:1-389.
Health Outcome(s) and Reported Health Effect(s):	Cancer/Carcinogenesis-Malignant lymphoma, histiocytic sarcoma, cardiac hemangio- sarcoma; harderian gland adenoma, hepatocellular adenoma and carcinoma, alveolarbronchiolar adenoma and carcinoma; mammary gland carcinoma, adenocanthoma, and malignant mixed tumor, benign and malignant ovarian granulosa cell tumor; and forestomach squamous cell papilloma and carcinoma, intestinal carcinomas, renal tubule adenomas, skin sarcomas, Zymbal's gland adenomas and carcinomas, lymphocytic lymphomas-Immune/Hematological-Histopathology: bone marrow, thymus, lymph nodes, spleen. Erythrocyte counts, hemoglobin concentration, packed red cell volume, mean erythrocyte volume, Organ weight: spleen and thymus-Reproductive/Developmental-Histopathology: testis, ovaries, uterus, mammary gland, seminal vesicle, epididymides, prostate gland, Organ weight: right testis-Gastrointestinal-Histopathology: stomach, small intestine, large intestine, gallbladder, salivary gland, esophagus-Lung/Respiratory-Histopathology: trachea, larynx, lung, pharynx, nose, Organ weight: lungs-Neurological/Behavioral-Histopathology: Brain, Organ weight: brain-Renal/Kidney-Histopathology: kidney. Creatine kinase in serum. Organ weight: right kidney-Hepatic/Liver-Histopathology: liver. Lactate dehydrogenase in serum, Organ weight: liver-Cardiovascular-Histopathology: Heart, Organ weight: heart-Musculoskeletal-Histopathology: sternebrae-Other (please specify below) (Endocrine)-Histopathology: Thyroid, parathyroid gland, pancreas, adrenal gland-Ocular/Sensory-Histopathology: Harderian gland Inhalation-Vapor-Duration: Chronic (>90 days)-5-6-52-week(s)-Inhalation-Vapor-Duration: Subchronic (>30-90 days)-5-6-13-week(s)
Duration and Exposure Route:	
Species:	Mouse-B6C3F1 - [mouse]-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	1419645

Domain	Metric	Rating	Comments
	Metric 5: Selective Reporting and Attrition	Medium	The authors report 1 accidental death and many natural deaths and exposure-related deaths over the course of the study. The natural deaths were unrelated to the exposure and are unlikely to significantly bias the results of the study. All outcomes described in the methods were reported in the results.

Domain 5: Exposure Methods Sensitivity

Metric 6: Chemical administration and characterization	Medium	The authors performed independent analytical verification of the test substance identity and purity and monitored exposure chamber concentrations during the exposure. Exposure characterization was redone every 3 months and the authors reported <5% variability in chamber concentrations. There are no concerns regarding the exposure chamber used. Test substance storage conditions were not described, but the authors state that 7 different lots of the chemical were used over the 2-year exposure period, which may have mitigated the potential effects of chemical instability over the course of the experiment.
Metric 7: Exposure timing, frequency, and duration	High	The exposure duration and frequency are sensitive to detect the endpoints of interest and does include the critical window of sensitivity for detecting health effects from chronic-duration exposures.

Domain 6: Outcome Measures and Results Display

Metric 8: Endpoint sensitivity and specificity	Low	The species is appropriate and there are no concerns regarding the specificity or sensitivity of the outcome assessment protocols. 50 animals were used for the main study groups, which is informative for detecting the endpoints of interest at chronic durations. The different exposure concentrations in this study were assessed at different times in order to test the hypothesis that effects would be directly related to the product of the exposure concentration times the duration of exposure. While this hypothesis has scientific merit, the inconsistency between exposure durations at different doses makes this experiment difficult to interpret for the sake of evaluating dose-response.
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Study Citation:	NTP, (1993). NTP Toxicology and Carcinogenesis Studies of 1,3-Butadiene (CAS No. 106-99-0) in B6C3F1 Mice (Inhalation Studies). National Toxicology Program Technical Report Series 434:1-389.
Health Outcome(s) and Reported Health Effect(s):	Cancer/Carcinogenesis-Malignant lymphoma, histiocytic sarcoma, cardiac hemangio- sarcoma; harderian gland adenoma, hepatocellular adenoma and carcinoma, alveolarbronchiolar adenoma and carcinoma; mammary gland carcinoma, adenoacanthoma, and malignant mixed tumor, benign and malignant ovarian granulosa cell tumor; and forestomach squamous cell papilloma and carcinoma, intestinal carcinomas, renal tubule adenomas, skin sarcomas, Zymbal's gland adenomas and carcinomas, lymphocytic lymphomas-Immune/Hematological-Histopathology: bone marrow, thymus, lymph nodes, spleen. Erythrocyte counts, hemoglobin concentration, packed red cell volume, mean erythrocyte volume, Organ weight: spleen and thymus-Reproductive/Developmental-Histopathology: testis, ovaries, uterus, mammary gland, seminal vesicle, epididymides, prostate gland, Organ weight: right testis-Gastrointestinal-Histopathology: stomach, small intestine, large intestine, gallbladder, salivary gland, esophagus-Lung/Respiratory-Histopathology: trachea, larynx, lung, pharynx, nose, Organ weight: lungs-Neurological/Behavioral-Histopathology: Brain, Organ weight: brain-Renal/Kidney-Histopathology: kidney. Creatine kinase in serum. Organ weight: right kidney-Hepatic/Liver-Histopathology: liver. Lactate dehydrogenase in serum, Organ weight: liver-Cardiovascular-Histopathology: Heart, Organ weight: heart-Musculoskeletal-Histopathology: sternebrae-Other (please specify below) (Endocrine)-Histopathology: Thyroid, parathyroid gland, pancreas, adrenal gland-Ocular/Sensory-Histopathology: Harderian gland Inhalation-Vapor-Duration: Chronic (>90 days)-5-6-52-week(s)-Inhalation-Vapor-Duration: Subchronic (>30-90 days)-5-6-13-week(s)
Duration and Exposure Route:	
Species:	Mouse-B6C3F1 - [mouse]-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	1419645

Domain	Metric	Rating	Comments
Metric 9:	Results presentation	High	The results presentation generally includes full quantitative presentation in figures and tables and qualitative descriptions in the text. Incidence for neoplastic and nonneoplastic lesions are reported and the statistical methods employed by the study authors are appropriate.

Overall Quality Determination**Medium**

Study Citation:	PNL., Battelle (1982). Initial submission: Tracor Jitco inhalation carcinogenesis bioassay: Chronic study report in 1,3-butadiene in mice (final report) with attachments and cover letter dated 112191.		
Health Outcome(s) and Reported Health Effect(s):	Other (please specify below) (Clinical signs)-Clinical signs		
Duration and Exposure Route:	Inhalation-Vapor-Duration: Chronic (>90 days)-5-6-61-week(s)		
Species:	Mouse-B6C3F1 - [mouse]-Both		
Chemical:	1,3-Butadiene- Parent compound		
HERO ID:	5554646		
Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	High	The test substance was identified as 1,3-Butadiene. The source was reported (Phillips Petroleum), purity was >99% pure based on independent gas chromatography. Test animal species, strain, sex, age, initial body weights, and source were reported. Husbandry conditions (temperature, humidity, light cycle, and number of animals/cage) were reported. Food and water were available ad libitum. The dose levels, frequency, duration, and route of exposure were reported. The target and actual concentrations were reported. Endpoint evaluation methods were reported along with quantitative data. All critical information and important information are reported.
Domain 2: Selection and Performance			
	Metric 2: Allocation	High	Animals were randomly assigned to study groups using computer-generated tables of random numbers. "Body weight was used as a blocking variable to ensure that no statistically significant differences existed in the group mean body weights."
	Metric 3: Observational Bias / Blinding Changes	Medium	Blinding or other measures to reduce observational bias were not reported; however, the endpoints are either not subjective (body weight), clinical signs, or are an initial histology review.
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	Uninformative	A sham-exposed negative control group was included. Sera was collected from 5 control males and females for murine virus antibody determination. 1/5 females tested positive for mouse hepatitis virus (all other antibody tests were negative). In the control mice, mononuclear perivascular cuffing in the lungs and mononuclear inflammation of the kidneys, salivary gland, and pancreas were observed and occurred more frequently than in the exposed mice. These increases in inflammatory responses in the control group could potentially confound results. In addition, the study reports males in the high dose group did not have food or water for 3 days during the treatment period, resulting in dehydration and considerable weight loss. Exposure was discontinued for a week while they recovered. Analysis of tap water was included, and findings were appropriate. Respiratory rate was not reported but the chemical is not expected to be a respiratory irritant.
Domain 4: Selective Reporting and Attrition			

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Study Citation:	PNL,, Battelle (1982). Initial submission: Tracor Jitco inhalation carcinogenesis bioassay: Chronic study report in 1,3-butadiene in mice (final report) with attachments and cover letter dated 112191.		
Health Outcome(s) and Reported Health Effect(s):	Other (please specify below) (Clinical signs)-Clinical signs		
Duration and Exposure Route:	Inhalation-Vapor-Duration: Chronic (>90 days)-5-6-61-week(s)		
Species:	Mouse-B6C3F1 - [mouse]-Both		
Chemical:	1,3-Butadiene- Parent compound		
HERO ID:	5554646		
Domain	Metric	Rating	Comments
Metric 5:	Selective Reporting and Attrition	Medium	All animals are accounted for in the body weight section (reported as died or with terminal body weight). Animals found dead or sacrificed moribund were reported at times, but not for every animal.
Domain 5: Exposure Methods Sensitivity			
Metric 6:	Chemical administration and characterization	Medium	The source and purity (>99%) of the test substance were reported. Target and actual concentrations were reported with variance. Generation of test substance vapor was reported adequately. Animals were exposed in a whole-body dynamic inhalation chamber. Since test substance may deposit on the fur for the animal during exposure and they may ingest the test substance during grooming, the study was downgraded to medium. The study reports that chamber flow and vacuum were maintained at 0.283 +/- 0.034 m3/min; the volume of the chamber was calculated to be 1.596 m3 based on reported cage dimensions (14.0 cm x 7.6 cm x 15.0 cm), therefore this reviewer calculated the number of air changes/ hour as 17. This is in-line with the recommended ≥ 10 air changes/hour.
Metric 7:	Exposure timing, frequency, and duration	High	In this inhalation study, the route and frequency were appropriate. The duration (61-62 weeks) is slightly less than the recommended 18 months for a carcinogenicity study however the study was stopped early because of the increased mortality. The exposure duration was long enough to see carcinogenic effects.
Domain 6: Outcome Measures and Results Display			
Metric 8:	Endpoint sensitivity and specificity	Medium	Outcome methodologies were sensitive to outcome of interest. Test animals were obtained from a commercial source. The number of animals/group was appropriate for carcinogenicity studies (50/sex/group). Animals were assessed consistently across study groups. The study did not report reasoning for choosing the concentrations studied. A full range of responses were not obtained (NOAEL could not be determined).
Metric 9:	Results presentation	High	Clinical signs are reported with the date the observations were made. Each animal is individually reported.

Overall Quality Determination**Uninformative**

Study Citation:	PNL,, Battelle (1982). Initial submission: Tracor Jitco inhalation carcinogenesis bioassay: Chronic study report in 1,3-butadiene in mice (final report) with attachments and cover letter dated 112191.		
Health Outcome(s) and Reported Health Effect(s):	Cancer/Carcinogenesis-Histopathology-Reproductive/Developmental-Histopathology on mammary gland, prostate, testes, ovaries, and uterus-Lung/Respiratory-Histopathology on lungs and mainstem bronchi, nasal cavity and nasal turbinates, trachea, pharynx (if grossly abnormal)-Cardiovascular-Histopathology on heart		
Duration and Exposure Route:	Inhalation-Vapor-Duration: Chronic (>90 days)-5-6-61-week(s)		
Species:	Mouse-B6C3F1 - [mouse]-Both		
Chemical:	1,3-Butadiene- Parent compound		
HERO ID:	5554646		
Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	High	The test substance was identified as 1,3-Butadiene. The source was reported (Phillips Petroleum), purity was >99% pure based on independent gas chromatography. Test animal species, strain, sex, age, initial body weights, and source were reported. Husbandry conditions (temperature, humidity, light cycle, and number of animals/cage) were reported. Food and water were available ad libitum. The dose levels, frequency, duration, and route of exposure were reported. The target and actual concentrations were reported. Endpoint evaluation methods were reported along with quantitative data. All critical information and important information are reported.
Domain 2: Selection and Performance			
	Metric 2: Allocation	High	Animals were randomly assigned to study groups using computer-generated tables of random numbers. "Body weight was used as a blocking variable to ensure that no statistically significant differences existed in the group mean body weights."
	Metric 3: Observational Bias / Blinding Changes	Medium	Blinding or other measures to reduce observational bias were not reported; however, the endpoints are either not subjective (body weight), clinical signs, or are an initial histology review.
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	Uninformative	A sham-exposed negative control group was included. Sera was collected from 5 control males and females for murine virus antibody determination. 1/5 females tested positive for mouse hepatitis virus (all other antibody tests were negative). In the control mice, mononuclear perivascular cuffing in the lungs and mononuclear inflammation of the kidneys, salivary gland, and pancreas were observed and occurred more frequently than in the exposed mice. These increases in inflammatory responses in the control group could potentially confound results. In addition, the study reports males in the high dose group did not have food or water for 3 days during the treatment period, resulting in dehydration and considerable weight loss. Exposure was discontinued for a week while they recovered. Analysis of tap water was included, and findings were appropriate. Respiratory rate was not reported but the chemical is not expected to be a respiratory irritant.
Domain 4: Selective Reporting and Attrition			
	Metric 5: Selective Reporting and Attrition	Low	Mortality was extremely high in the exposure groups (38-88%) compared to controls (2-8%). Time of death or what the animal died from is not reported for all animals. Because incidence data is not reported, it cannot be determined if all treated animals were included in analysis.

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Study Citation:	PNL,, Battelle (1982). Initial submission: Tracor Jitco inhalation carcinogenesis bioassay: Chronic study report in 1,3-butadiene in mice (final report) with attachments and cover letter dated 112191.		
Health Outcome(s) and Reported Health Effect(s):	Cancer/Carcinogenesis-Histopathology-Reproductive/Developmental-Histopathology on mammary gland, prostate, testes, ovaries, and uterus-Lung/Respiratory-Histopathology on lungs and mainstem bronchi, nasal cavity and nasal turbinates, trachea, pharynx (if grossly abnormal)-Cardiovascular-Histopathology on heart		
Duration and Exposure Route:	Inhalation-Vapor-Duration: Chronic (>90 days)-5-6-61-week(s)		
Species:	Mouse-B6C3F1 - [mouse]-Both		
Chemical:	1,3-Butadiene- Parent compound		
HERO ID:	5554646		
Domain	Metric	Rating	Comments
Domain 5: Exposure Methods Sensitivity			
Metric 6:	Chemical administration and characterization	Medium	The source and purity (>99%) of the test substance were reported. Target and actual concentrations were reported with variance. Generation of test substance vapor was reported adequately. Animals were exposed in a whole-body dynamic inhalation chamber. Since test substance may deposit on the fur of the animal during exposure and they may ingest the test substance during grooming, the study was downgraded to medium. The study reports that chamber flow and vacuum were maintained at 0.283 +/- 0.034 m ³ /min; the volume of the chamber was calculated to be 1.596 m ³ based on reported cage dimensions (14.0 cm x 7.6 cm x 15.0 cm), therefore this reviewer calculated the number of air changes/ hour as 17. This is in-line with the recommended ≥10 air changes/hour.
Metric 7:	Exposure timing, frequency, and duration	High	In this inhalation study, the route and frequency were appropriate. The duration (61-62 weeks) is slightly less than the recommended 18 months for a carcinogenicity study however the study was stopped early because of the increased mortality. The exposure duration was long enough to see carcinogenic effects.
Domain 6: Outcome Measures and Results Display			
Metric 8:	Endpoint sensitivity and specificity	Medium	Outcome methodologies were sensitive to outcome of interest. Test animals were obtained from a commercial source. The number of animals/group was appropriate for carcinogenicity studies (50/sex/group). Animals were assessed consistently across study groups. The study did not report reasoning for choosing the concentrations studied. A full range of responses were not obtained (NOAEL could not be determined).
Metric 9:	Results presentation	Low	Histological data is described in text without incidence data. The study reports statistical significance in text but does not disclose which tests were used. Data are not presented in such a way that independent statistics could be performed. The study states that "only positive histopathological findings were tabulated", therefore we assume organs without any data were negative for lesions.

Overall Quality Determination**Uninformative**

Study Citation:	PNL,, Battelle (1982). Initial submission: Tracor Jitco inhalation carcinogenesis bioassay: Chronic study report in 1,3-butadiene in mice (final report) with attachments and cover letter dated 112191.		
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Body weight		
Duration and Exposure Route:	Inhalation-Vapor-Duration: Chronic (>90 days)-5-6-61-week(s)		
Species:	Mouse-B6C3F1 - [mouse]-Both		
Chemical:	1,3-Butadiene- Parent compound		
HERO ID:	5554646		
Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	High	The test substance was identified as 1,3-Butadiene. The source was reported (Phillips Petroleum), purity was >99% pure based on independent gas chromatography. Test animal species, strain, sex, age, initial body weights, and source were reported. Husbandry conditions (temperature, humidity, light cycle, and number of animals/cage) were reported. Food and water were available ad libitum. The dose levels, frequency, duration, and route of exposure were reported. The target and actual concentrations were reported. Endpoint evaluation methods were reported along with quantitative data. All critical information and important information are reported.
Domain 2: Selection and Performance			
	Metric 2: Allocation	High	Animals were randomly assigned to study groups using computer-generated tables of random numbers. "Body weight was used as a blocking variable to ensure that no statistically significant differences existed in the group mean body weights."
	Metric 3: Observational Bias / Blinding Changes	Medium	Blinding or other measures to reduce observational bias were not reported; however, the endpoints are either not subjective (body weight), clinical signs, or are an initial histology review.
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	Uninformative	A sham-exposed negative control group was included. Sera was collected from 5 control males and females for murine virus antibody determination. 1/5 females tested positive for mouse hepatitis virus (all other antibody tests were negative). In the control mice, mononuclear perivascular cuffing in the lungs and mononuclear inflammation of the kidneys, salivary gland, and pancreas were observed and occurred more frequently than in the exposed mice. These increases in inflammatory responses in the control group could potentially confound results. In addition, the study reports males in the high dose group did not have food or water for 3 days during the treatment period, resulting in dehydration and considerable weight loss. Exposure was discontinued for a week while they recovered. Some females also went blind due to pushing their head through mesh of the cage Analysis of tap water was included, and findings were appropriate. Respiratory rate was not reported but the chemical is not expected to be a respiratory irritant.
Domain 4: Selective Reporting and Attrition			
	Metric 5: Selective Reporting and Attrition	High	All animals are accounted for in the body weight section (reported as died or with terminal body weight). Animals found dead or sacrificed moribund were reported at times, but not for every animal.

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Study Citation:	PNL,, Battelle (1982). Initial submission: Tracor Jitco inhalation carcinogenesis bioassay: Chronic study report in 1,3-butadiene in mice (final report) with attachments and cover letter dated 112191.		
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Body weight		
Duration and Exposure Route:	Inhalation-Vapor-Duration: Chronic (>90 days)-5-6-61-week(s)		
Species:	Mouse-B6C3F1 - [mouse]-Both		
Chemical:	1,3-Butadiene- Parent compound		
HERO ID:	5554646		
Domain	Metric	Rating	Comments
Domain 5: Exposure Methods Sensitivity			
Metric 6:	Chemical administration and characterization	Medium	The source and purity (>99%) of the test substance were reported. Target and actual concentrations were reported with variance. Generation of test substance vapor was reported adequately. Animals were exposed in a whole-body dynamic inhalation chamber. Since test substance may deposit on the fur of the animal during exposure and they may ingest the test substance during grooming, the study was downgraded to medium. The study reports that chamber flow and vacuum were maintained at 0.283 +/- 0.034 m ³ /min; the volume of the chamber was calculated to be 1.596 m ³ based on reported cage dimensions (14.0 cm x 7.6 cm x 15.0 cm), therefore this reviewer calculated the number of air changes/ hour as 17. This is in-line with the recommended ≥10 air changes/hour.
Metric 7:	Exposure timing, frequency, and duration	High	In this inhalation study, the route and frequency were appropriate. The duration (61-62 weeks) is slightly less than the recommended 18 months for a carcinogenicity study however the study was stopped early because of the increased mortality. The exposure duration was long enough to see carcinogenic effects.
Domain 6: Outcome Measures and Results Display			
Metric 8:	Endpoint sensitivity and specificity	Medium	Outcome methodologies were sensitive to outcome of interest. Test animals were obtained from a commercial source. The number of animals/group was appropriate for carcinogenicity studies (50/sex/group). Animals were assessed consistently across study groups. The study did not report reasoning for choosing the concentrations studied. A full range of responses were not obtained (NOAEL could not be determined).
Metric 9:	Results presentation	Low	Initial body weights were presented for all animals. Terminal body weights were presented for animals that survived to the end of the 61-62 weeks, however there is not adequate reporting of body weights throughout the study. After the males in the high dose group were accidentally deprived of food and water for 3 days, the authors do report some information on body weight recovery, but only for one date (10/14/81) and only in males.

Overall Quality Determination**Uninformative**

Study Citation:	Thurmond, L. M., Lauer, L. D., House, R. V., Stillman, W. S., Irons, R. D., Steinhagen, W. H., Dean, J. H. (1986). Effects of short-term inhalation exposure to 1,3-butadiene on murine immune functions. <i>Toxicology and Applied Pharmacology</i> 86(2):170-179.
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Body weights
Duration and Exposure Route:	Inhalation-Gas-Duration: Subchronic (>30-90 days)-5-6-12-week(s)-Inhalation-Gas-Duration: Chronic (>90 days)-5-6-24-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	62366

Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	Medium	All critical and most important information were reported. B6C3F1 mice (sex and source, age, initial body weights provided) were exposed whole-body to 1,3-butadiene (source, purity, composition reported). Details of caging, the inhalation chamber, and the number of animals per group (reported in results), were described. Animal husbandry (food and water availability, light cycle, and animals per cage) details were reported. Outcome assessment methods and results for all outcomes were reported. Missing information included: mouse age and initial body weights; temperature, humidity, and details of atmosphere generation.
Domain 2: Selection and Performance			
	Metric 2: Allocation	Low	The method of animal allocation into groups was not specified. The study did not specify whether animals were normalized to body weights.
	Metric 3: Observational Bias / Blinding Changes	Medium	Blinding was not specified; however, the potential for bias was mitigated because the endpoints were not considered to be subjective in nature.
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	Medium	A concurrent negative control group was exposed to filtered air only. The control responses were appropriate. Initial body weights and some animal husbandry conditions were not reported (e.g., temperature, humidity) and consistency among groups cannot be determined. Respiratory rates were not measured in an inhalation study. However, the test material is considered to be a respiratory irritant in humans, but not in animals.
Domain 4: Selective Reporting and Attrition			
	Metric 5: Selective Reporting and Attrition	Low	The number of animals exposed per group per duration was not described in the methods. The results table specifies the sample size to be 5-6 rats, but it is unclear whether all animals were accounted for in the results. Mortality was not assessed/ reported in subchronic and chronic duration studies. The methods do not clearly indicate when some endpoints were measured (e.g., the methods indicate that body weights were weighed, but not whether body weights were weighed in animals from all three exposure durations); data for longer durations were not reported. It is unclear whether any animal attrition occurred.
Domain 5: Exposure Methods Sensitivity			

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Study Citation:	Thurmond, L. M., Lauer, L. D., House, R. V., Stillman, W. S., Irons, R. D., Steinhagen, W. H., Dean, J. H. (1986). Effects of short-term inhalation exposure to 1,3-butadiene on murine immune functions. <i>Toxicology and Applied Pharmacology</i> 86(2):170-179.
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Body weights
Duration and Exposure Route:	Inhalation-Gas-Duration: Subchronic (>30-90 days)-5-6-12-week(s)-Inhalation-Gas-Duration: Chronic (>90 days)-5-6-24-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	62366

Domain	Metric	Rating	Comments
Metric 6:	Chemical administration and characterization	Low	1,3-butadiene was procured from Exxon Corp in several intervals/batches. The purity of all batches was monitored using GC and was >99.5%. The concentration of dimer 4-vinyl-1-cyclohexane was ≤165 ppm. Dimer concentrations in the chambers were < 0.21 ppm. Atmosphere generation methods, including the equipment used, were not described. Animals were exposed whole-body in a dynamic chamber; the number of air changes per hour and the number of animals in each chamber were not specified. Concentrations in the chambers were monitored continuously with an infrared spectrophotometer. The reported concentration is presumed to be the target. No analytical values were provided, and it was not specified if the measured values were close to target or nominal concentrations. The authors justified the concentration tested, which was intended to mimic human occupational exposure. 1,250 ppm was reported as the short-term threshold limit value for human exposure.
Metric 7:	Exposure timing, frequency, and duration	High	The study used three durations: 6 weeks, 12 weeks and 24 weeks. The study introduction indicated that previous studies showed the appearance of murine thymic lymphomas following 20 weeks of exposure. This study aimed to identify functional immune system changes that may occur at earlier time points. Therefore, the three durations tested were appropriate for the purposes of the study and also for this outcome of interest. Additionally, animals were exposed 6hrs/day, 5 days/week which is typical for subchronic/chronic inhalation toxicity studies.

Domain 6: Outcome Measures and Results Display

Metric 8:	Endpoint sensitivity and specificity	Low	Body weights were only purportedly measured once at the time of sacrifice, which is atypical for subchronic/chronic duration studies, and the timing is not sensitive enough to assess potential changes throughout the exposure periods. The methods also do not specify whether body weights were measured in animals from all exposure-duration groups. The test animal species was appropriate and justified, but only males were used without further justification. The single exposure group was appropriate for this study, which tested three different durations. Sample sizes were noted in Table 1 which reports body weight data for the 6-week duration groups.
Metric 9:	Results presentation	Medium	The statistical method (Dunnett's modification of Student's T test for multiple comparisons) was reported. Since the methods did not adequately specify which endpoints were measured at each duration, it is difficult to determine whether the results reported were adequate (e.g., if results for body weight measurements of animals exposed for 12 or 24 weeks were missing). Of the results shown, the data were quantitatively reported as means ± SE.

Overall Quality Determination

Low

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Study Citation:	Thurmond, L. M., Lauer, L. D., House, R. V., Stillman, W. S., Irons, R. D., Steinhagen, W. H., Dean, J. H. (1986). Effects of short-term inhalation exposure to 1,3-butadiene on murine immune functions. <i>Toxicology and Applied Pharmacology</i> 86(2):170-179.
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Body weights
Duration and Exposure Route:	Inhalation-Gas-Duration: Subchronic (>30-90 days)-5-6-12-week(s)-Inhalation-Gas-Duration: Chronic (>90 days)-5-6-24-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	62366

Domain	Metric	Rating	Comments

Study Citation:	Thurmond, L. M., Lauer, L. D., House, R. V., Stillman, W. S., Irons, R. D., Steinhagen, W. H., Dean, J. H. (1986). Effects of short-term inhalation exposure to 1,3-butadiene on murine immune functions. <i>Toxicology and Applied Pharmacology</i> 86(2):170-179.		
Health Outcome(s) and Reported Health Effect(s):	Immune/Hematological-Organ weights (spleen and thymus); histopathology (spleen and thymus); functional immune assays (humoral immunity: antibody plaque-forming cell (PFC) response, cell-mediated immunity: mitogen-stimulated alloantigens lymphocyte proliferation assay and mixed lymphocyte cultures); Mechanistic (non-apical) endpoints (cellularities of spleen and bone marrow; analysis of splenocyte surface markers; immunolabeling of splenocytes; lymphocyte proliferation and cytotoxicity to alloantigens; spontaneous natural killer cell cytotoxicity).		
Duration and Exposure Route:	Inhalation-Gas-Duration: Chronic (>90 days)-5-6-24-week(s)		
Species:	Mouse-B6C3F1 - [mouse]-Male		
Chemical:	1,3-Butadiene- Parent compound		
HERO ID:	62366		
Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
Metric 1:	Reporting Quality	Medium	All critical and most important information were reported. B6C3F1 mice (sex and source, age, initial body weights provided) were exposed whole-body to 1,3-butadiene (source, purity, composition reported). Details of caging, the inhalation chamber, and the number of animals per group (reported in results), were described. Animal husbandry (food and water availability, light cycle, and animals per cage) details were reported. Outcome assessment methods and results for all outcomes were reported. Missing information included: mouse age and initial body weights; temperature, humidity, and details of atmosphere generation.
Domain 2: Selection and Performance			
Metric 2:	Allocation	Low	The method of animal allocation into groups was not specified. The study did not specify whether animals were normalized to body weights.
Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not specified; however, the potential for bias was mitigated because the endpoints were not considered to be subjective in nature.
Domain 3: Confounding / Variable Control			
Metric 4:	Confounding / Variable Control	Medium	A concurrent negative control group was exposed to filtered air only. The control responses were appropriate. There are no specific guidelines available for most of the immunotoxicity endpoints tested. It is unclear whether a positive control would have been reasonable, particularly in cases with no observed effects. Initial body weights and some animal husbandry conditions were not reported (e.g., temperature, humidity) and consistency among groups cannot be determined. Respiratory rates were not measured in an inhalation study. However, the test material is considered to be a respiratory irritant in humans, but not in animals.
Domain 4: Selective Reporting and Attrition			
Metric 5:	Selective Reporting and Attrition	Low	The number of animals exposed per group per duration was not described in the methods, and results for only some of the endpoints specified the sample sizes. It is unclear whether all animals were accounted for in the results. Mortality was not reported in sub-chronic and chronic duration studies. The methods do not clearly indicate when some endpoints were measured (e.g., organ weights), and these results were reported for the 6-week exposure duration only.
Domain 5: Exposure Methods Sensitivity			

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Study Citation:	Thurmond, L. M., Lauer, L. D., House, R. V., Stillman, W. S., Irons, R. D., Steinhagen, W. H., Dean, J. H. (1986). Effects of short-term inhalation exposure to 1,3-butadiene on murine immune functions. <i>Toxicology and Applied Pharmacology</i> 86(2):170-179.		
Health Outcome(s) and Reported Health Effect(s):	Immune/Hematological-Organ weights (spleen and thymus); histopathology (spleen and thymus); functional immune assays (humoral immunity: antibody plaque-forming cell (PFC) response, cell-mediated immunity: mitogen-stimulated alloantigens lymphocyte proliferation assay and mixed lymphocyte cultures); Mechanistic (non-apical) endpoints (cellularities of spleen and bone marrow; analysis of splenocyte surface markers; immunolabeling of splenocytes; lymphocyte proliferation and cytotoxicity to alloantigens; spontaneous natural killer cell cytotoxicity).		
Duration and Exposure Route:	Inhalation-Gas-Duration: Chronic (>90 days)-5-6-24-week(s)		
Species:	Mouse-B6C3F1 - [mouse]-Male		
Chemical:	1,3-Butadiene- Parent compound		
HERO ID:	62366		
Domain	Metric	Rating	Comments
Metric 6:	Chemical administration and characterization	Low	1,3-butadiene was procured from Exxon Corp in several intervals/batches. The purity of all batches was monitored using GC and was >99.5%. The concentration of dimer 4-vinyl-1-cyclohexane was \leq 165 ppm. Dimer concentrations in the chambers were < 0.21 ppm. Atmosphere generation methods, including the equipment used, were not described. Animals were exposed whole-body in a dynamic chamber; the number of air changes per hour and the number of animals in each chamber were not specified. Concentrations in the chambers were monitored continuously with an infrared spectrophotometer. The reported concentration is presumed to be the target. No analytical values were provided, and it was not specified if the measured values were close to target or nominal concentrations. The authors justified the concentration tested, which was intended to mimic human occupational exposure. 1,250 ppm was reported as the short-term threshold limit value for human exposure.
Metric 7:	Exposure timing, frequency, and duration	High	The study used three durations: 6 weeks, 12 weeks and 24 weeks. The study introduction indicated that previous studies showed the appearance of murine thymic lymphomas following 20 weeks of exposure. This study aimed to identify functional immune system changes that may occur at earlier time points. Therefore, the three durations tested were appropriate for the purposes of the study. Additionally, animals were exposed 6hrs/day, 5 days/week which is typical for subchronic/chronic inhalation toxicity studies.
Domain 6: Outcome Measures and Results Display	Metric 8: Endpoint sensitivity and specificity	Low	This study evaluated a limited, but focused number of endpoints which spanned both <i>in vivo</i> and downstream <i>in vitro</i> evaluations of changes to immune-related organs and functional immune responses. The protocols for each test were generally described, with citations provided for further information for most. The study did not clearly indicate which endpoints were evaluated in which exposure-duration groups. The tests were sensitive for the outcomes of interest although limitations for some tests were described (e.g., it was noted that there are no reliable cell surface markers for enumerating erythroid cell populations, and mitogen responses may have been fewer due to the use of unpurified splenocytes). It was also noted in several places in the text that tumors were observed in previous studies after 20 weeks of exposure. This study exposed one group of animals for 24 weeks but did not assess or mention whether any tumors were observed. The test animal species was appropriate and justified, but only males were used without further justification. The single exposure group was appropriate for this study, which tested three different durations. The study did not adequately describe or report group or sample sizes. Sample sizes in Figure 1 were not specified. Sufficient methodological details were not provided to determine consistency across groups.

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Study Citation:	Thurmond, L. M., Lauer, L. D., House, R. V., Stillman, W. S., Irons, R. D., Steinhagen, W. H., Dean, J. H. (1986). Effects of short-term inhalation exposure to 1,3-butadiene on murine immune functions. <i>Toxicology and Applied Pharmacology</i> 86(2):170-179.
Health Outcome(s) and Reported Health Effect(s):	Immune/Hematological-Organ weights (spleen and thymus); histopathology (spleen and thymus); functional immune assays (humoral immunity: antibody plaque-forming cell (PFC) response, cell-mediated immunity: mitogen-stimulated alloantigens lymphocyte proliferation assay and mixed lymphocyte cultures); Mechanistic (non-apical) endpoints (cellularities of spleen and bone marrow; analysis of splenocyte surface markers; immunolabeling of splenocytes; lymphocyte proliferation and cytotoxicity to alloantigens; spontaneous natural killer cell cytotoxicity).
Duration and Exposure Route:	Inhalation-Gas-Duration: Chronic (>90 days)-5-6-24-week(s)
Species:	Mouse-B6C3F1 - [mouse]-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	62366

Domain	Metric	Rating	Comments
	Metric 9: Results presentation	Uninformative	The statistical method (Dunnett's modification of Student's T test for multiple comparisons) was reported. Since the methods did not adequately specify which endpoints were measured at each duration, it is difficult to determine whether the results reported were adequate. The reporting of histopathology, the only result shown for this exposure duration, was insufficient. Only a representative image is provided; changes were described in the text with no reporting of incidences or whether the incidences were statistically significant from controls. These data are uninformative and do not allow the ability to adequately assess this outcome.

Overall Quality Determination

Uninformative

Study Citation:	Anderson, D., Hughes, J. A., Edwards, A. J., Brinkworth, M. H. (1998). A comparison of male-mediated effects in rats and mice exposed to 1,3-butadiene. Mutation Research 397(1):77-84.
Health Outcome(s) and Reported	Reproductive/Developmental-Reproductive endpoints: (mating frequency, % pregnant)Developmental endpoints (Number of implantations, number of live fetuses, number of post-implantation loss including early and late resorptions, number of fetuses with gross malformations, cytogenetic analysis of fetal livers)-Nutritional/Metabolic-Parental body weights-Other (please specify below) (Genotoxicity)-Dominant lethality-Mortality-Parental death
Health Effect(s):	
Duration and Exposure Route:	Inhalation-Gas-Duration: Reproductive/Developmental-1-F0- pre-mating (4 weeks)
Species:	Mouse-CD-1 - [mouse]-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	1327602

Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	Medium	All critical and most important information was provided. CD-1 mice (sex, source, and age were reported) were exposed to 1,3-butadiene (source and purity reported) via whole-body inhalation to the test material gas at 0, 12.5, 65, and 130 ppm for 6 hrs/day, 5 days/week for 4 weeks (25 males/group). Animal starting body weights and parity were not specified. All animal husbandry details (temperature, humidity, lighting, food and water availability, and the number of animals per cage) were specified. All endpoint evaluation methods were described, and/or citations were provided for additional procedural details. Quantitative or qualitative results were reported for at least one endpoint of interest.
Domain 2: Selection and Performance			
	Metric 2: Allocation	Medium	Both male and female animals were randomly assigned to groups, but the method of randomization was not reported. It was also not specified whether animals were normalized to body weights.
	Metric 3: Observational Bias / Blinding Changes	Medium	The study did not report blinding or other methods/procedures for reducing observational bias; however, the outcomes were not subjective in nature and blinding was not required.
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	Medium	Some details to determine whether there was confounding between groups were missing. Animal body weights were not reported and respiration rate was not monitored in an inhalation study. The test material is considered to be a respiratory irritant in humans (PubChem), but not in animals. The study utilized an appropriate negative control (ambient air only) and the responses of the negative controls were appropriate. According to OECD TG 478, positive controls should always be used unless the testing laboratory has demonstrated proficiency in the conduct of the test. This laboratory referenced several previous studies using the same methods.
Domain 4: Selective Reporting and Attrition			

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Study Citation:	Anderson, D., Hughes, J. A., Edwards, A. J., Brinkworth, M. H. (1998). A comparison of male-mediated effects in rats and mice exposed to 1,3-butadiene. Mutation Research 397(1):77-84.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Reproductive endpoints: (mating frequency, % pregnant)Developmental endpoints (Number of implantations, number of live fetuses, number of post-implantation loss including early and late resorptions, number of fetuses with gross malformations, cytogenetic analysis of fetal livers)-Nutritional/Metabolic-Parental body weights-Other (please specify below) (Genotoxicity)-Dominant lethality-Mortality-Parental death
Duration and Exposure Route:	Inhalation-Gas-Duration: Reproductive/Developmental-1-F0- premating (4 weeks)
Species:	Mouse-CD-1 - [mouse]-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	1327602

Domain	Metric	Rating	Comments
Metric 5:	Selective Reporting and Attrition	High	1-2 male mice in each treatment group and no control rats died due to injuries; however, the numbers of deaths were small and are not expected to have a significant impact on the study results. Quantitative or qualitative statements were made for all endpoints, and quantitative data were provided for all exposure groups. The sample sizes were reported for most outcomes and were similar across groups. There is no indication of selective reporting.

Domain 5: Exposure Methods Sensitivity

Metric 6:	Chemical administration and characterization	Low	The test material was obtained from ICI plc, Wilton, UK. The supplier's website could not be located, but it was reported in the study that a certificate of analysis was provided by the supplier and the purity was 99.73%. The study methods referred to the test material as "BD", but the title of the paper specified it was 1,3-butadiene. Although the purity was high, it was indicated that the [exposure] cylinders contained at most 0.5% of the dimer 4 vinyl-1-cyclohexane. The test material was stored at -20 degrees for long-term storage and at 4 degrees between exposures. No details on the generation of the exposure atmospheres were provided; exposure chambers were described as sealed glass chambers that contained stainless steel grid chambers, each containing one mouse. It was not specified if they were static or dynamic. The exposure concentrations (presumed target) were reported in the study abstract, but no analytical measurements of atmospheres were described. The missing details regarding the exposure parameters result in significant uncertainty.
Metric 7:	Exposure timing, frequency, and duration	Medium	The exposure timing, frequency, and duration were justified by the study authors and based on exposures in previous studies. It was specified that the duration of exposure covered the sensitive stages of the spermatogenic cycle that were known to induce early deaths in previous studies. However, the authors later noted in the discussion that a longer duration may be required to produce effects on late deaths or fetal abnormalities., which were not seen in this study.

Domain 6: Outcome Measures and Results Display

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Study Citation:	Anderson, D., Hughes, J. A., Edwards, A. J., Brinkworth, M. H. (1998). A comparison of male-mediated effects in rats and mice exposed to 1,3-butadiene. Mutation Research 397(1):77-84.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Reproductive endpoints: (mating frequency, % pregnant)Developmental endpoints (Number of implantations, number of live fetuses, number of post-implantation loss including early and late resorptions, number of fetuses with gross malformations, cytogenetic analysis of fetal livers)-Nutritional/Metabolic-Parental body weights-Other (please specify below) (Genotoxicity)-Dominant lethality-Mortality-Parental death
Duration and Exposure Route:	Inhalation-Gas-Duration: Reproductive/Developmental-1-F0- premating (4 weeks)
Species:	Mouse-CD-1 - [mouse]-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	1327602

Domain	Metric	Rating	Comments
	Metric 8: Endpoint sensitivity and specificity	Low	This was a non-guideline modified dominant lethal study. The purpose of the study was to both confirm findings related to malformations from a previous 10-week study in mice and also to test a lower dose range that was representative of levels humans males were exposed to in the workplace. The number of exposure groups, (n = 3 plus a control), and the concentration spacing were justified by the authors and were adequate to address the purpose of the study. The endpoints were primarily focused on fetal death; however, more sensitive endpoints including examinations for skeletal malformations in all animals/group could have been included. The outcome assessment methods were adequately described in some cases. No details of body weight measurements (e.g., what animals and the timing/frequency) or on mating frequency or duration were provided in the methods. However, it was noted in a table legend that mice were mated for up to one week. Typically, sequential weekly matings are conducted (e.g., 4 weekly matings are required after a 28-day exposure) so that all phases of spermatogenesis are evaluated, or single matings are appropriate if exposure covers the full window of spermatogenesis which is ~7 weeks for mice) (OECD TG 428). Additionally, details of the sampling for skeletal analysis were confusing/not clearly reported. The text states that "malformed fetuses, randomly selected normal litter mates and controls" were also investigated for selected malformations... and cytogenetic analysis. Based on this statement, It is unclear whether skeletal examinations were conducted on fetuses with gross malformations or on those that were normal. Evaluations were conducted on all treatment groups. The animal model was appropriate, and animals were obtained from a commercial source. The sample sizes were sufficient for most outcomes; however, the sampling for skeletal examinations was not reported in the methods, and the study discussion mentioned sampling of 10, 2, 1, and 4 animals in the control, low, mid, and high-exposure groups, respectively. It is unclear why the sample sizes were different across groups, and the low numbers preclude the ability to do statistical analysis or draw any conclusions about the results.
	Metric 9: Results presentation	Low	Statistical methods were adequately described for all endpoints. It is unclear whether statistical tests considered the male as the experimental unit as specified by OECD TG 478. It was noted that statistical analysis of skeletal examination data was not appropriate because only select fetuses, rather than the total population were examined. Some results were quantitatively reported as incidences or means \pm SD, but negative findings (no effects observed) for parental body weights, mating and pregnancy frequencies, and cytogenetic analysis were qualitatively described in the text. The data for skeletal examinations were not shown and the text only stated that the results confirmed the macroscopic abnormalities seen. Further description of any skeletal malformations should have been included.

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Study Citation:	Anderson, D., Hughes, J. A., Edwards, A. J., Brinkworth, M. H. (1998). A comparison of male-mediated effects in rats and mice exposed to 1,3-butadiene. Mutation Research 397(1):77-84.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Reproductive endpoints: (mating frequency, % pregnant)Developmental endpoints (Number of implantations, number of live fetuses, number of post-implantation loss including early and late resorptions, number of fetuses with gross malformations, cytogenetic analysis of fetal livers)-Nutritional/Metabolic-Parental body weights-Other (please specify below) (Genotoxicity)-Dominant lethality-Mortality-Parental death
Duration and Exposure Route:	Inhalation-Gas-Duration: Reproductive/Developmental-1-F0- premating (4 weeks)
Species:	Mouse-CD-1 - [mouse]-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	1327602

Domain	Metric	Rating	Comments
Overall Quality Determination		Medium	

Study Citation:	Anderson, D., Hughes, J. A., Edwards, A. J., Brinkworth, M. H. (1998). A comparison of male-mediated effects in rats and mice exposed to 1,3-butadiene. Mutation Research 397(1):77-84.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Reproductive endpoints: (mating frequency, % pregnant)Developmental endpoints (Number of implantations, number of live fetuses, number of post-implantation loss including early and late resorptions, number of fetuses with gross malformations, cytogenetic analysis of fetal livers)-Nutritional/Metabolic-Parental body weights-Other (please specify below) (Genotoxicity)-Dominant lethality-Mortality-Parental death
Duration and Exposure Route:	Inhalation-Gas-Duration: Reproductive/Developmental-1-F0- premating (10 weeks)
Species:	Rat-Sprague-Dawley - [rat]-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	1327602

Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	Medium	All critical and most important information was provided. Sprague Dawley rats (sex, source, and age were reported) were exposed to 1,3-butadiene (source and purity reported) via whole-body inhalation to the test material gas at 0, 65, 400, and 1,250 ppm for 6 hrs/day, 5 days/week for 10 weeks (25 males/group plus additional controls. Animal starting body weights and parity were not specified. All animal husbandry details (temperature, humidity, lighting, food and water availability, and the number of animals per cage) were specified. All endpoint evaluation methods were described, and/or citations were provided for additional procedural details. Quantitative or qualitative results were reported for at least one endpoint of interest.
Domain 2: Selection and Performance			
	Metric 2: Allocation	Medium	Both male and female animals were randomly assigned to groups, but the method of randomization was not reported. It was also not specified whether animals were normalized to body weights.
	Metric 3: Observational Bias / Blinding Changes	Medium	The study did not report blinding or other methods/procedures for reducing observational bias; however, the outcomes were not subjective in nature and blinding was not required.
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	Medium	Some details to determine whether there was confounding between groups were missing. Animal body weights were not reported and respiration rate was not monitored in an inhalation study. The test material is considered to be a respiratory irritant in humans (PubChem), but not in animals. The study utilized an appropriate negative control (ambient air only) and the responses of the negative controls were appropriate. In addition to the concurrent control group, a double set of other control animals were kept in standard room air in free-standing cage racks to control for any effects resulting from stress caused to animals due to enclosure in the inhalation chambers. According to OECD TG 478, positive controls should always be used unless the testing laboratory has demonstrated proficiency in the conduct of the test. This laboratory referenced several previous studies using the same methods.
Domain 4: Selective Reporting and Attrition			
	Metric 5: Selective Reporting and Attrition	High	One male in the low-exposure group died. There was no evidence of animal attrition. Quantitative or qualitative statements were made for all endpoints, and quantitative data were provided for all exposure groups. The sample sizes were reported and were similar across groups. There is no evidence of selective reporting.

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Study Citation:	Anderson, D., Hughes, J. A., Edwards, A. J., Brinkworth, M. H. (1998). A comparison of male-mediated effects in rats and mice exposed to 1,3-butadiene. Mutation Research 397(1):77-84.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Reproductive endpoints: (mating frequency, % pregnant)Developmental endpoints (Number of implantations, number of live fetuses, number of post-implantation loss including early and late resorptions, number of fetuses with gross malformations, cytogenetic analysis of fetal livers)-Nutritional/Metabolic-Parental body weights-Other (please specify below) (Genotoxicity)-Dominant lethality-Mortality-Parental death
Duration and Exposure Route:	Inhalation-Gas-Duration: Reproductive/Developmental-1-F0- premating (10 weeks)
Species:	Rat-Sprague-Dawley - [rat]-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	1327602

Domain	Metric	Rating	Comments
Domain 5: Exposure Methods Sensitivity			
	Metric 6: Chemical administration and characterization	Low	The test material was obtained from ICI plc, Wilton, UK. The supplier's website could not be located, but it was reported in the study that a certificate of analysis was provided by the supplier and the purity was 99.5%. The study methods referred to the test material as "BD", but the title of the paper specified it was 1,3-butadiene. Although the purity was high, it was indicated that the [exposure] cylinders contained at most 0.5% of the dimer 4 vinyl-1-cyclohexane. The test material was stored at -20 degrees for long-term storage and at 4 degrees between exposures. No details on the generation of the exposure atmospheres were provided; exposure chambers were described as sealed glass chambers that contained stainless steel grid chambers, each containing one mouse. It was not specified if they were static or dynamic. The exposure concentrations (presumed target) were reported in the study abstract, but no analytical measurements of atmospheres were described. The missing details regarding the exposure parameters result in significant uncertainty.
	Metric 7: Exposure timing, frequency, and duration	High	Although the purpose of the study was to determine if there were any species differences, the rats were exposed for 10 weeks rather than 4 weeks (duration of mouse exposure). This allowed comparison to 10-week mouse data generated previously. The authors stated that this duration would allow for a better comparison of malformations.

Domain 6: Outcome Measures and Results Display

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Study Citation:	Anderson, D., Hughes, J. A., Edwards, A. J., Brinkworth, M. H. (1998). A comparison of male-mediated effects in rats and mice exposed to 1,3-butadiene. Mutation Research 397(1):77-84.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Reproductive endpoints: (mating frequency, % pregnant)Developmental endpoints (Number of implantations, number of live fetuses, number of post-implantation loss including early and late resorptions, number of fetuses with gross malformations, cytogenetic analysis of fetal livers)-Nutritional/Metabolic-Parental body weights-Other (please specify below) (Genotoxicity)-Dominant lethality-Mortality-Parental death
Duration and Exposure Route:	Inhalation-Gas-Duration: Reproductive/Developmental-1-F0- premating (10 weeks)
Species:	Rat-Sprague-Dawley - [rat]-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	1327602

Domain	Metric	Rating	Comments
	Metric 8: Endpoint sensitivity and specificity	Low	This was a non-guideline modified dominant lethal study. The purpose of the study was to conduct a species comparison with mice. The number of exposure groups, (n = 3 plus two sets of controls), and the concentration spacing were not explicitly justified by the authors. No effects were observed, even at the highest concentration; however, the high concentration was the same one used in the previous 10-week mouse study, so for comparison purposes, the concentrations tested were appropriate and show that there are species differences. The outcome assessment methods were adequately described in some cases. Details on the frequency of body weight measurements were also not provided. Mating details were not provided in the methods, but a table legend indicated that males cohabitated with females for up to 9 days. Typically, sequential weekly matings are conducted (e.g., 4 weekly matings are required after a 28-day exposure) so that all phases of spermatogenesis are evaluated. However, because the exposure duration for this study was so long (10 weeks) and the goal was simply to detect dominant lethality, then the single mating was likely appropriate. The endpoints were primarily focused on fetal death; however, more sensitive endpoints including examinations for skeletal malformations could have been included, although these are not typically required in dominant lethality tests. Evaluations were conducted on all treatment groups. The animal model was appropriate and the animals were obtained from a commercial source. The sample size (n = 48-50 females mated to 24-25 males) was sufficient.
	Metric 9: Results presentation	Medium	Statistical methods were adequately described for all endpoints. It is unclear whether the male was used as the experimental unit as specified in OECD TG 478. Some results were quantitatively reported as incidences or means \pm SD, but negative findings (no effects observed) for parental body weights, and mating and pregnancy frequencies were qualitatively described in the text.

Overall Quality Determination**Medium**

Study Citation:	BIBRA, (1996). Initial submission: the detection of dominant lethal mutations and * in the offspring of male mice treated subchronically with butadiene by inhalation, w/cover letter dated 1/10/97.
Health Outcome(s) and Reported	Mortality-Mortality in parental animals-Nutritional/Metabolic-Weekly body weights (males); Body weights females
Health Effect(s):	
Duration and	
Exposure Route:	
Species:	Mouse-CD-1 - [mouse]-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	5665017

Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	High	All critical and most important information, was provided. Sprague Dawley rats (sex, source, and age were reported) were exposed to 1,3-butadiene (source and purity reported) via whole-body inhalation to the test material gas at 0, 65, 400, and 1,250 ppm for 6 hrs/day, 5 days/week for 4 weeks (50 males/group). Animal starting body weights were reported for both sexes; the females were nulliparous. All animal husbandry details (temperature, humidity, lighting, food and water availability, number of animals per cage) were specified. All endpoint evaluation methods were described, and/or citations were provided for additional procedural details. Quantitative results were reported for at least one endpoint of interest.
Domain 2: Selection and Performance			
	Metric 2: Allocation	Medium	Both male and female animals were randomly assigned to groups; however, the method of randomization was not specified. It was also not specified whether animals were normalized to body weights but animals were weighed upon arrival.
	Metric 3: Observational Bias / Blinding Changes	Medium	The study did not report blinding or other methods/procedures for reducing observational bias; however, the outcomes were not subjective in nature and blinding was not required.
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	Medium	The study included an air-only control. Positive controls were not included; however, the laboratory cited previous publications using the same methods that showed positive responses. There were issues with the thermohygrometer during the first week of exposure. This is not expected to have a significant impact on the study results. The authors noted a considerable variation in temperature (21.7-25.9 degrees C), and humidity (17-64%) between study days and chambers. It is unclear whether these variations had any impact on the study results. It was noted that confirmation of pregnancy via vaginal plug was not determined in >50% of females, and therefore the gestation day was not accurately known. Therefore, effects at the end of gestation (number of late deaths, dead fetuses, and abnormal fetuses) may have been underestimated, but it is not expected that this would have an impact on body weight or mortality. Respiratory rates were not monitored in an inhalation study; however, there is no conclusive evidence that the test material is a respiratory irritant.

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Study Citation:	BIBRA, (1996). Initial submission: the detection of dominant lethal mutations and * in the offspring of male mice treated subchronically with butadiene by inhalation, w/cover letter dated 1/10/97.		
Health Outcome(s) and Reported Health Effect(s):	Mortality-Mortality in parental animals-Nutritional/Metabolic-Weekly body weights (males); Body weights females		
Duration and Exposure Route:	Inhalation-Gas-Duration: Reproductive/Developmental-1-F0- premating (4 weeks)		
Species:	Mouse-CD-1 - [mouse]-Male		
Chemical:	1,3-Butadiene- Parent compound		
HERO ID:	5665017		

Domain	Metric	Rating	Comments
Domain 4: Selective Reporting and Attrition			
	Metric 5: Selective Reporting and Attrition	High	Quantitative results were provided for almost all outcomes. Fetal body weights were not reported; however, they were used to identify runts. All animals were healthy at the start of the study. There was no evidence of animal attrition. The authors explained or justified the exclusion of any animals from analysis.
Domain 5: Exposure Methods Sensitivity			
	Metric 6: Chemical administration and characterization	Low	The test material was obtained from ICI plc, Wilton, UK. The supplier website could not be located, but it was reported in the study that a certificate of analysis was provided by the supplier for each batch and the purity was 99.73%. The purity for two cylinders was 99.59%. The dimer content was also tested and was between 1 and 437 ppm. The test material was supplied weekly and stored at -20 degrees for long-term storage, and at 4 degrees between exposures. Animals were exposed whole-body. The method of atmosphere generation and exposure chamber details were described. The test substance (as a gas) was diluted with dry air; generally, humidified air is used for diluting gases unless the substance is water-reactive. Sealed glass chambers contained stainless steel grid chambers, each containing one mouse. The description was suggestive of a dynamic chamber; however, the number of air changes/hour was not specified. The exposure atmospheres were continuously monitored and analyzed for test substance content using infrared spectrophotometry and were considered acceptable if kept within 15% of the target. The authors noted that there were some instances when concentrations were outside 15% due to misconnected tubing. The authors also noted that the variance in the lower butadiene concentrations may be due to the method used to dilute the neat material. It was stated that "the daily exposure period (normally 6 h) approximately comprised a ~2 minute build-up period from 0 ppm to the required concentration, a 5* h period of constant concentration and a 12 minute period in which the concentration returned to 0 ppm before removing the animals from the cages. The range of concentrations received during the nominally constant period ranged from zero to approximately three times the required concentration." The unacceptable concentrations were corrected as quickly as possible. Measured concentrations are reported, but overall mean measured concentrations were not provided. The authors stated that they did not expect any fluctuations to have a significant impact on the overall concentrations or the study results.
	Metric 7: Exposure timing, frequency, and duration	High	Males were exposed for a total of 4 weeks prior to mating. This duration was justified by the authors and was based on the results of previous studies from the current and other laboratories. There are no concerns about the exposure timing, frequency, and duration for the outcomes selected.

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Study Citation:	BIBRA, (1996). Initial submission: the detection of dominant lethal mutations and * in the offspring of male mice treated subchronically with butadiene by inhalation, w/cover letter dated 1/10/97.
Health Outcome(s) and Reported Health Effect(s):	Mortality-Mortality in parental animals-Nutritional/Metabolic-Weekly body weights (males); Body weights females
Duration and Exposure Route:	Inhalation-Gas-Duration: Reproductive/Developmental-1-F0- premating (4 weeks)
Species:	Mouse-CD-1 - [mouse]-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	5665017

Domain	Metric	Rating	Comments
Domain 6: Outcome Measures and Results Display			
	Metric 8: Endpoint sensitivity and specificity	High	This was a non-guideline modified dominant lethal study. The purpose of the study was to conduct a species comparison with rats and to confirm the results of previous studies in the same species. The number of exposure groups, (n = 3 plus a control), and the concentration spacing were justified by the authors and based on previous studies. Evaluations were conducted on all treatment groups. The endpoints were primarily focused on post-implantation death; however, the modified study design also allowed for the testing of male-mediated fetal malformations. The protocols/methods for the outcomes/endpoint specified (mortality, body weights) were appropriate and sensitive to the outcomes of interest. Sufficient methodological details (e.g., frequency of observations or measurements) were reported. The animal model was justified and animals were obtained from a commercial source. The sample sizes for these outcomes (n = approximately 50/sex) were sufficient.
	Metric 9: Results presentation	High	Results for the outcomes specified were clearly reported. Where appropriate, means \pm SD were provided, and individual animal data were included in appendices. The methods of statistical analysis were clearly described and were appropriate for the datasets.

Overall Quality Determination**Medium**

Study Citation:	BIBRA, (1996). Initial submission: the detection of dominant lethal mutations and * in the offspring of male mice treated subchronically with butadiene by inhalation, w/cover letter dated 1/10/97.		
Health Outcome(s) and Reported Health Effect(s):	Other (please specify below) (Daily observations)-Observations for deviations from normal		
Duration and Exposure Route:	Inhalation-Gas-Duration: Reproductive/Developmental-1-F0- premating (4 weeks)		
Species:	Mouse-CD-1 - [mouse]-Male		
Chemical:	1,3-Butadiene- Parent compound		
HERO ID:	5665017		
Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
Metric 1: Reporting Quality	High	All critical and most important information, was provided. Sprague Dawley rats (sex, source, and age were reported) were exposed to 1,3-butadiene (source and purity reported) via whole-body inhalation to the test material gas at 0, 65, 400, and 1,250 ppm for 6 hrs/day, 5 days/week for 4 weeks (50 males/group). Animal starting body weights were reported for both sexes; the females were nulliparous. All animal husbandry details (temperature, humidity, lighting, food and water availability, number of animals per cage) were specified. All endpoint evaluation methods were described, and/or citations were provided for additional procedural details. Quantitative results were reported for at least one endpoint of interest.	
Domain 2: Selection and Performance			
Metric 2: Allocation	Medium	Both male and female animals were randomly assigned to groups; however, the method of randomization was not specified. It was also not specified whether animals were normalized to body weights but animals were weighed upon arrival.	
Metric 3: Observational Bias / Blinding Changes	Medium	The study did not report blinding or other methods/procedures for reducing observational bias; blinding was not reported for clinical signs	
Domain 3: Confounding / Variable Control			
Metric 4: Confounding / Variable Control	Medium	The study included an air-only control. Positive controls were not included; however, the laboratory cited previous publications using the same methods that showed positive responses. There were issues with the thermohygrometer during the first week of exposure. This is not expected to have a significant impact on the study results. The authors noted a considerable variation in temperature (21.7-25.9 degrees C), and humidity (17-64%) between study days and chambers. It is unclear whether these variations had any impact on the study results. It was noted that confirmation of pregnancy via vaginal plug was not determined in >50% of females, and therefore the gestation day was not accurately known. Therefore, effects at the end of gestation (number of late deaths, dead fetuses, and abnormal fetuses) may have been underestimated, but it is not expected that this would have an impact on this outcome. Respiratory rates were not monitored in an inhalation study; however, there is no conclusive evidence that the test material is a respiratory irritant.	
Domain 4: Selective Reporting and Attrition			

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Study Citation: BIBRA, (1996). Initial submission: the detection of dominant lethal mutations and * in the offspring of male mice treated subchronically with butadiene by inhalation, w/cover letter dated 1/10/97.

Health Outcome(s) and Reported Health Effect(s): Other (please specify below) (Daily observations)-Observations for deviations from normal

Duration and Exposure Route: Inhalation-Gas-Duration: Reproductive/Developmental-1-F0- premating (4 weeks)

Species: Mouse-CD-1 - [mouse]-Male

Chemical: 1,3-Butadiene- Parent compound

HERO ID: 5665017

Domain	Metric	Rating	Comments
	Metric 5: Selective Reporting and Attrition	Low	Fetal body weights were not reported; however, they were used to identify runts. Results for clinical signs were not reported. All animals were healthy at the start of the study. There was no evidence of animal attrition. The authors explained or justified the exclusion of any animals from the analysis.

Domain 5: Exposure Methods Sensitivity

Metric 6: Chemical administration and characterization	Low	The test material was obtained from ICI plc, Wilton, UK. The supplier website could not be located, but it was reported in the study that a certificate of analysis was provided by the supplier for each batch and the purity was 99.73%. The purity for two cylinders was 99.59%. The dimer content was also tested and was between 1 and 437 ppm. The test material was supplied weekly and stored at -20 degrees for long-term storage, and at 4 degrees between exposures. Animals were exposed whole-body. The method of atmosphere generation and exposure chamber details were described. The test substance (as a gas) was diluted with dry air; generally, humidified air is used for diluting gases unless the substance is water-reactive. Sealed glass chambers contained stainless steel grid chambers, each containing one mouse. The description was suggestive of a dynamic chamber; however, the number of air changes/hour was not specified. The exposure atmospheres were continuously monitored and analyzed for test substance content using infrared spectrophotometry and were considered acceptable if kept within 15% of the target. The authors noted that there were some instances when concentrations were outside 15% due to misconnected tubing. The authors also noted that the variance in the lower butadiene concentrations may be due to the method used to dilute the neat material. It was stated that "the daily exposure period (normally 6 h) approximately comprised a ~2 minute build-up period from 0 ppm to the required concentration, a 5* h period of constant concentration and a 12 minute period in which the concentration returned to 0 ppm before removing the animals from the cages. The range of concentrations received during the nominally constant period ranged from zero to approximately three times the required concentration." The unacceptable concentrations were corrected as quickly as possible. Measured concentrations are reported, but overall mean measured concentrations were not provided. The authors stated that they did not expect any fluctuations to have a significant impact on the overall concentrations or the study results.
Metric 7: Exposure timing, frequency, and duration	High	Males were exposed for a total of 4 weeks prior to mating. This duration was justified by the authors and was based on the results of previous studies from the current and other laboratories. There are no concerns about the exposure timing, frequency, and duration for the outcomes selected.

Domain 6: Outcome Measures and Results Display

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Study Citation: BIBRA, (1996). Initial submission: the detection of dominant lethal mutations and * in the offspring of male mice treated subchronically with butadiene by inhalation, w/cover letter dated 1/10/97.

Health Outcome(s) and Reported Health Effect(s): Other (please specify below) (Daily observations)-Observations for deviations from normal

Duration and Exposure Route: Inhalation-Gas-Duration: Reproductive/Developmental-1-F0- premating (4 weeks)

Species: Mouse-CD-1 - [mouse]-Male

Chemical: 1,3-Butadiene- Parent compound

HERO ID: 5665017

Domain	Metric	Rating	Comments
Metric 8:	Endpoint sensitivity and specificity	Medium	This was a non-guideline modified dominant lethal study. The purpose of the study was to conduct a species comparison with rats and to also confirm results from previous studies in the same species. The number of exposure groups, (n = 3 plus a control), and the concentration spacing were justified by the authors and based on previous studies. Evaluations were conducted on all treatment groups. The endpoints were primarily focused on post-implantation death; however, the modified study design also allowed for the testing of male-mediated fetal malformations. The protocol/methods indicated that animals were observed twice daily (am and pm) and constantly during treatment but the nature of the observations were not specified (e.g., cage side or detailed clinical signs). The animal model was justified and animals were obtained from a commercial source. However, the authors did note that there is a significant formation of butadiene diepoxide in mice compared with other species, and the effects observed may be unique to mice. The sample sizes for these outcomes (n = approximately 50/sex) were sufficient. Results for clinical observations (either positive or negative) were not reported.
Metric 9:	Results presentation	Uninformative	

Overall Quality Determination

Uninformative

Study Citation:	BIBRA, (1996). Initial submission: the detection of dominant lethal mutations and * in the offspring of male mice treated subchronically with butadiene by inhalation, w/cover letter dated 1/10/97.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Reproductive/Developmental-Mating frequency, pregnancy rate, period of coition, number of corpora lutea, number of live and dead implantations, post-implantation loss (early and late deaths, dead fetuses), fetal sex, body weights of live fetuses, gross malformations, skeletal examinations-Other (please specify below) (Dominant Lethality)-Dominant lethality
Duration and Exposure Route:	Inhalation-Gas-Duration: Reproductive/Developmental-1-F0- premating (4 weeks)
Species:	Mouse-CD-1 - [mouse]-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	5665017

Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	High	All critical and most important information, was provided. Sprague Dawley rats (sex, source, and age were reported) were exposed to 1,3-butadiene (source and purity reported) via whole-body inhalation to the test material gas at 0, 65, 400, and 1,250 ppm for 6 hrs/day, 5 days/week for 4 weeks (50 males/group). Animal starting body weights were reported for both sexes; the females were nulliparous. All animal husbandry details (temperature, humidity, lighting, food and water availability, number of animals per cage) were specified. All endpoint evaluation methods were described, and/or citations were provided for additional procedural details. Quantitative results were reported for at least one endpoint of interest.
Domain 2: Selection and Performance			
	Metric 2: Allocation	Medium	Both male and female animals were randomly assigned to groups; however, the method of randomization was not specified. It was also not specified whether animals were normalized to body weights but animals were weighed upon arrival.
	Metric 3: Observational Bias / Blinding Changes	Medium	The study did not report blinding or other methods/procedures for reducing observational bias; however, the outcomes were not subjective in nature and blinding was not required.
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	Low	The study included an air-only control. Positive controls were not included; however, the laboratory cited previous publications using the same methods that showed positive responses. There were issues with the thermohygrometer during the first week of exposure. This is not expected to have a significant impact on the study results. The authors noted a considerable variation in temperature (21.7-25.9 degrees C), and humidity (17-64%) between study days and chambers. It is unclear whether these variations had any impact on the study results. It was noted that confirmation of pregnancy via vaginal plug was not determined in >50% of females, and therefore the gestation day was not accurately known. Therefore, effects including time to coition, and at the end of gestation (number of late deaths, dead fetuses, and abnormal fetuses) may have been underestimated. The authors noted that the variance in the lower butadiene concentrations may be due to the method used to dilute the neat material. Respiratory rates were not monitored in an inhalation study; however, there is no conclusive evidence that the test material is a respiratory irritant.
Domain 4: Selective Reporting and Attrition			

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Study Citation:	BIBRA, (1996). Initial submission: the detection of dominant lethal mutations and * in the offspring of male mice treated subchronically with butadiene by inhalation, w/cover letter dated 1/10/97.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Reproductive/Developmental-Mating frequency, pregnancy rate, period of coition, number of corpora lutea, number of live and dead implantations, post-implantation loss (early and late deaths, dead fetuses), fetal sex, body weights of live fetuses, gross malformations, skeletal examinations-Other (please specify below) (Dominant Lethality)-Dominant lethality
Duration and Exposure Route:	Inhalation-Gas-Duration: Reproductive/Developmental-1-F0- premating (4 weeks)
Species:	Mouse-CD-1 - [mouse]-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	5665017

Domain	Metric	Rating	Comments
Metric 5:	Selective Reporting and Attrition	High	Quantitative results were provided for almost all outcomes. Fetal body weights were not reported; however, they were used to identify runts. Results for clinical signs were not reported. All animals were healthy at the start of the study. There was no evidence of animal attrition. The authors explained or justified the exclusion of any animals from the analysis.

Domain 5: Exposure Methods Sensitivity

Metric 6:	Chemical administration and characterization	Low	The test material was obtained from ICI plc, Wilton, UK. The supplier website could not be located, but it was reported in the study that a certificate of analysis was provided by the supplier for each batch and the purity was 99.73%. The purity for the two cylinders was 99.59%. The dimer content was also tested and was between 1 and 437 ppm. The test material was supplied weekly and stored at -20 degrees for long-term storage, and at 4 degrees between exposures. Animals were exposed whole-body. The method of atmosphere generation and exposure chamber details were described. The test substance (as a gas) was diluted with dry air; generally, humidified air is used for diluting gases unless the substance is water-reactive. Sealed glass chambers contained stainless steel grid chambers, each containing one mouse. The description was suggestive of a dynamic chamber; however, the number of air changes/hour was not specified. The exposure atmospheres were continuously monitored and analyzed for test substance content using infrared spectrophotometry and were considered acceptable if kept within 15% of the target. The authors noted that there were some instances when concentrations were outside 15% due to misconnected tubing. The authors also noted that the variance in the lower butadiene concentrations may be due to the method used to dilute the neat material. It was stated that "the daily exposure period (normally 6 h) approximately comprised a ~2 minute build-up period from 0 ppm to the required concentration, a 5* h period of constant concentration and a 12 minute period in which the concentration returned to 0 ppm before removing the animals from the cages. The range of concentrations received during the nominally constant period ranged from zero to approximately three times the required concentration." The unacceptable concentrations were corrected as quickly as possible. Measured concentrations are reported, but overall mean measured concentrations were not provided. The authors stated that they did not expect any fluctuations to have a significant impact on the overall concentrations or the study results.
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Study Citation:	BIBRA, (1996). Initial submission: the detection of dominant lethal mutations and * in the offspring of male mice treated subchronically with butadiene by inhalation, w/cover letter dated 1/10/97.		
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Reproductive/Developmental-Mating frequency, pregnancy rate, period of coition, number of corpora lutea, number of live and dead implantations, post-implantation loss (early and late deaths, dead fetuses), fetal sex, body weights of live fetuses, gross malformations, skeletal examinations-Other (please specify below) (Dominant Lethality)-Dominant lethality		
Duration and Exposure Route:	Inhalation-Gas-Duration: Reproductive/Developmental-1-F0- premating (4 weeks)		
Species:	Mouse-CD-1 - [mouse]-Male		
Chemical:	1,3-Butadiene- Parent compound		
HERO ID:	5665017		

Domain	Metric	Rating	Comments
	Metric 7: Exposure timing, frequency, and duration	Medium	Males were exposed for a total of 4 weeks prior to mating. This duration was justified by the authors and was based on the results of previous studies from the current and other laboratories. However, the authors noted that reducing the duration of exposure to 4 weeks from 10 weeks (the duration in their previous study), may have reduced the ability to detect dominant lethal mutations at the lower exposure concentrations. OECD TG 478 suggests exposure for 7 weeks followed by a single mating at the end.

Domain 6: Outcome Measures and Results Display

Metric 8: Endpoint sensitivity and specificity	Medium	This was a non-guideline modified dominant lethal study. The purpose of the study was to conduct a species comparison with rats and to also confirm results from previous studies in the same species. The number of exposure groups, (n = 3 plus a control), and the concentration spacing were justified by the authors and based on previous studies. Evaluations were conducted on all treatment groups. The endpoints were primarily focused on post-implantation death; however, the modified study design also allowed for the testing of male-mediated fetal malformations. Detailed methods for the reproductive/developmental and dominant lethality endpoints were provided and were consistent with those typically included for this study type. Skeletal examinations were only conducted on "select individuals," those identified as runts, and an equal number of normal fetuses per group, as well as a matched normal control. In some cases, examinations were done on only 2-4 fetuses/group. Due to the small numbers and wide variance across groups, these data could not be statistically analyzed. The sample sizes for other endpoints (n = 48-50 females mated to 24-25 males) were sufficient. The animal model was appropriate and animals were obtained from a commercial source.
Metric 9: Results presentation	High	Results for the outcomes specified were reported. Where appropriate, means \pm SD were provided, and individual animal data were included in appendices. The methods of statistical analysis were clearly described and were appropriate for the datasets.

Overall Quality Determination**Medium**

Study Citation:	BIBRA, (1996). Initial submission: the detection of dominant lethal mutations and * in the offspring of male mice treated subchronically with butadiene by inhalation, w/cover letter dated 1/10/97.
Health Outcome(s) and Reported Health Effect(s):	Other (please specify below) (Genotoxicity)-Chromosome aberrations/ karyotyping in fetuses
Duration and Exposure Route:	Inhalation-Gas-Duration: Reproductive/Developmental-1-F0- premating (4 weeks)
Species:	Mouse-CD-1 - [mouse]-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	5665017

Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	High	All critical and most important information, was provided. Sprague Dawley rats (sex, source, and age were reported) were exposed to 1,3-butadiene (source and purity reported) via whole-body inhalation to the test material gas at 0, 65, 400, and 1,250 ppm for 6 hrs/day, 5 days/week for 4 weeks (50 males/group). Animal starting body weights were reported for both sexes; the females were nulliparous. All animal husbandry details (temperature, humidity, lighting, food and water availability, number of animals per cage) were specified. All endpoint evaluation methods were described, and/or citations were provided for additional procedural details. Quantitative results were reported for at least one endpoint of interest.
Domain 2: Selection and Performance			
	Metric 2: Allocation	Medium	Both male and female animals were randomly assigned to groups; however, the method of randomization was not specified. It was also not specified whether animals were normalized to body weights but animals were weighed upon arrival.
	Metric 3: Observational Bias / Blinding Changes	Medium	The study did not report blinding or other methods/procedures for reducing observational bias; however, the outcomes were not subjective in nature and blinding was not required.
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	Low	The study included an air-only control. Positive controls were not included; the laboratory cited a previous publication by the same laboratory that also conducted karyotyping, but the results were negative and there was no mention of a positive control. There were issues with the thermohygrometer during the first week of exposure. This is not expected to have a significant impact on the study results. The authors noted a considerable variation in temperature (21.7-25.9 degrees C), and humidity (17-64%) between study days and chambers. It is unclear whether these variations had any impact on the study results. It was noted that confirmation of pregnancy via vaginal plug was not determined in >50% of females, and therefore the gestation day was not accurately known. Therefore, effects at the end of gestation (number of late deaths, dead fetuses, and abnormal fetuses) may have been underestimated. This may not have had a significant impact on this endpoint. Respiratory rates were not monitored in an inhalation study; however, there is no conclusive evidence that the test material is a respiratory irritant.
Domain 4: Selective Reporting and Attrition			

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Study Citation:	BIBRA, (1996). Initial submission: the detection of dominant lethal mutations and * in the offspring of male mice treated subchronically with butadiene by inhalation, w/cover letter dated 1/10/97.		
Health Outcome(s) and Reported Health Effect(s):	Other (please specify below) (Genotoxicity)-Chromosome aberrations/ karyotyping in fetuses		
Duration and Exposure Route:	Inhalation-Gas-Duration: Reproductive/Developmental-1-F0- premating (4 weeks)		
Species:	Mouse-CD-1 - [mouse]-Male		
Chemical:	1,3-Butadiene- Parent compound		
HERO ID:	5665017		

Domain	Metric	Rating	Comments
Metric 5:	Selective Reporting and Attrition	High	Quantitative results were provided for almost all outcomes. Fetal body weights were not reported; however, they were used to identify runts. Results for clinical signs were not reported. All animals were healthy at the start of the study. There was no evidence of animal attrition. The authors explained or justified the exclusion of any animals from the analysis.

Domain 5: Exposure Methods Sensitivity

Metric 6:	Chemical administration and characterization	Low	The test material was obtained from ICI plc, Wilton, UK. The supplier website could not be located, but it was reported in the study that a certificate of analysis was provided by the supplier for each batch and the purity was 99.73%. The purity for the two cylinders was 99.59%. The dimer content was also tested and was between 1 and 437 ppm. The test material was supplied weekly and stored at -20 degrees for long-term storage, and at 4 degrees between exposures. Animals were exposed whole-body. The method of atmosphere generation and exposure chamber details were described. The test substance (as a gas) was diluted with dry air; generally, humidified air is used for diluting gases unless the substance is water-reactive. Sealed glass chambers contained stainless steel grid chambers, each containing one mouse. The description was suggestive of a dynamic chamber; however, the number of air changes/hour was not specified. The exposure atmospheres were continuously monitored and analyzed for test substance content using infrared spectrophotometry and were considered acceptable if kept within 15% of the target. The authors noted that there were some instances when concentrations were outside 15% due to misconnected tubing. The authors also noted that the variance in the lower butadiene concentrations may be due to the method used to dilute the neat material. It was stated that "the daily exposure period (normally 6 h) approximately comprised a ~2 minute build-up period from 0 ppm to the required concentration, a 5* h period of constant concentration and a 12 minute period in which the concentration returned to 0 ppm before removing the animals from the cages. The range of concentrations received during the nominally constant period ranged from zero to approximately three times the required concentration." The unacceptable concentrations were corrected as quickly as possible. Measured concentrations are reported, but overall mean measured concentrations were not provided. The authors stated that they did not expect any fluctuations to have a significant impact on the overall concentrations or the study results.
Metric 7:	Exposure timing, frequency, and duration	Medium	Males were exposed for a total of 4 weeks prior to mating. This duration was justified by the authors and was based on the results of previous studies from the current and other laboratories. However, the authors noted that reducing the duration of exposure to 4 weeks from 10 weeks (the duration in their previous study), may have reduced the ability to detect dominant lethal mutations at the lower exposure concentrations.

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Study Citation:	BIBRA, (1996). Initial submission: the detection of dominant lethal mutations and * in the offspring of male mice treated subchronically with butadiene by inhalation, w/cover letter dated 1/10/97.
Health Outcome(s) and Reported Health Effect(s):	Other (please specify below) (Genotoxicity)-Chromosome aberrations/ karyotyping in fetuses
Duration and Exposure Route:	Inhalation-Gas-Duration: Reproductive/Developmental-1-F0- premating (4 weeks)
Species:	Mouse-CD-1 - [mouse]-Male
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	5665017

Domain	Metric	Rating	Comments
Domain 6: Outcome Measures and Results Display			
	Metric 8: Endpoint sensitivity and specificity	Low	<p>This was a non-guideline modified dominant lethal study. The purpose of the study was to conduct a species comparison with rats and to also confirm results from previous studies in the same species. The number of exposure groups, (n = 3 plus a control), and the concentration spacing were justified by the authors and based on previous studies. Evaluations were conducted on all treatment groups. The endpoints were primarily focused on post-implantation death; however, the modified study design also allowed for the testing of male-mediated fetal malformations. This outcome (chromosome damage) is not required for the study type and was done in addition to the standard dominant lethality assessment, but was noted as a main focus of the paper. The protocol was sensitive to the outcome of interest and methodological details were clearly reported. However, the sample sizes were inconsistent across groups. Karyotyping was conducted only on fetuses identified as runts along with a single normal fetus from the same litter. In total the assessment was conducted on 2 runts/14 normal control fetuses (from 10 litters), 2 runts/2 normal fetuses (2 litters) in the 12.5 ppm group, 1 runt/1 normal fetus from the 65 ppm group, and 6 runts/6 normal fetuses (4 litters) in the 130 ppm group. The animal model was justified and animals were obtained from a commercial source. However, the authors note that the genotoxic effects reported in mice in this study may not be anticipated in other species, due in part to the significant formation of butadiene diepoxide in mice, which is minimally formed in other species.</p>
	Metric 9: Results presentation	Low	<p>Karyotype results were adequately reported for the animals tested. No statistical methods were described for this endpoint, which was only a summary table of qualitative karyotype descriptions and was not very sensitive to identifying DNA damage. Additionally, only two metaphases were analyzed per animal.</p>

Overall Quality Determination**Low**

Study Citation:	Hazleton Labs, (1981). 1,3-Butadiene: Inhalation teratogenicity study in the rat (Final report).		
Health Outcome(s) and Reported	Mortality-Mortality and morbidity (dams)-Nutritional/Metabolic-Dam body weights, body weight gain-Reproductive/Developmental-Gravid uterine weights, numbers of corpora lutea, implantations (along with positions), live fetuses, early and late deaths, live fetal body weights, crown/rump length, external, visceral, and skeletal examinations.		
Health Effect(s):	Inhalation-Gas-Duration: Reproductive/Developmental-1-F0 - gestation (GD 6-15)		
Duration and Exposure Route:	Inhalation-Gas-Duration: Reproductive/Developmental-1-F0 - gestation (GD 6-15)		
Species:	Rat-Sprague-Dawley - [rat]-Female		
Chemical:	1,3-Butadiene- Parent compound		
HERO ID:	62371		
Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
Metric 1:	Reporting Quality	Medium	Quantitative data for all endpoints and exposure groups were provided. Summary tables for continuous data did not include measures of variance or an "N" to indicate sample size; however, individual animal data for all endpoints were provided in appendices. Statistical methods were clearly described and were appropriate for the datasets (the litter was used as the experimental unit where appropriate). Descriptions of severity were included for the fetal defects observed.
Domain 2: Selection and Performance			
Metric 2:	Allocation	Medium	Pregnant dams were allocated into exposure groups according to body weight. This was not combined with any other randomization procedure.
Metric 3:	Observational Bias / Blinding Changes	Medium	No blinding was described; however, the endpoints evaluated were either simple measures, or not subjective in nature.
Domain 3: Confounding / Variable Control			
Metric 4:	Confounding / Variable Control	Low	The study included air-only chamber controls. A positive control group was also included to demonstrate the sensitivity of the animal strain used; however, positive controls are generally not required for the study type. Respiratory rates were not reported for an inhalation study, but there is no conclusive data that the test substance is a respiratory irritant. Some fluctuations in temperature and humidity occurred that were outside of the acceptable range; however, these changes were attributed to inaccuracies of the instruments. The study authors noted several deviations between the controls used in this study and background/historical controls from the same laboratory. For example, control fetuses in this study were smaller (mean fetal weight and crown/rump length) than normal, and control animals showed low incidences of wavy ribs. This was considered to be unusual as incidences of wavy ribs are rarely found (1 incidence in 3,228 historical controls). These confounding factors make it difficult to interpret the study results. The authors opted to dismiss some statistically significant effects, attributing them to the noted differences in the animals used compared to normal.
Domain 4: Selective Reporting and Attrition			
Metric 5:	Selective Reporting and Attrition	High	Quantitative data for all endpoints and exposure groups were provided. There is no indication of selective reporting. All animals were healthy at the start of the exposure period. There is no information to suggest the presence of animal attrition.

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Study Citation:	Hazleton Labs, (1981). 1,3-Butadiene: Inhalation teratogenicity study in the rat (Final report).		
Health Outcome(s) and Reported Health Effect(s):	Mortality-Mortality and morbidity (dams)-Nutritional/Metabolic-Dam body weights, body weight gain-Reproductive/Developmental-Gravid uterine weights, numbers of corpora lutea, implantations (along with positions), live fetuses, early and late deaths, live fetal body weights, crown/rump length, external, visceral, and skeletal examinations.		
Duration and Exposure Route:	Inhalation-Gas-Duration: Reproductive/Developmental-1-F0 - gestation (GD 6-15)		
Species:	Rat-Sprague-Dawley - [rat]-Female		
Chemical:	1,3-Butadiene- Parent compound		
HERO ID:	62371		

Domain	Metric	Rating	Comments
Domain 5: Exposure Methods Sensitivity			
	Metric 6: Chemical administration and characterization	Low	The test substance was identified as 1,3-butadiene and was supplied by the study sponsor. The test substance was analyzed by the sponsor before sending, and samples were collected during and after the study period for additional analysis. The purity of the test substance was not explicitly reported. However, the analysis data provided reports concentrations of all impurities, so a general idea of purity can be determined. Samples were also analyzed for the presence of the 4-vinyl-1-cyclohexane dimer and the butadiene inhibitor (tertiary butyl-catechol)concentrations; concentrations fell within acceptable ranges. Details of atmosphere generation and the exposure chambers were provided. The process of volatilization was described; however, the study referred to the test substance as both a vapor and a gas seemingly interchangeably. Storage details were provided. The exposure atmospheres were monitored continuously for test substance concentration via GC. The analytical mean of chamber concentrations was provided. The inhalation route was justified by the study authors. Animals were exposed whole-body via inhalation in a dynamic chamber. The number of air changes (7.5-9.0 changes/hour) was lower than preferred (10/hr), which warrants a score of LOW; the flow rate was reported.
	Metric 7: Exposure timing, frequency, and duration	Medium	Animals were exposed for 6 hrs/day, from GD 6-15, which may not include the window of sensitivity for the endpoints evaluated. Exposure should begin on GD 5 to measure the effects on implantation and continue through GD 19 to measure skeletal effects. The exposure administration was consistent across groups.

Domain 6: Outcome Measures and Results Display			
	Metric 8: Endpoint sensitivity and specificity	High	The study did not cite a specific guideline, but was generally consistent with an OECD 414 prenatal developmental toxicity study and the endpoints measured were sensitive to the outcomes of interest. The exposure groups and spacing were set by the sponsors and justified. The test model was appropriate and justified by the study authors; susceptibility was demonstrated through the use of a positive control. The methods were adequately described and sampling was adequate to allow for statistical analysis.
	Metric 9: Results presentation	Medium	Quantitative data for all endpoints and exposure groups were provided. Summary tables for continuous data did not include measures of variance or an "N" to indicate sample size; however, individual animal data for all endpoints were provided in appendices. Statistical methods were clearly described and were appropriate for the datasets (the litter was used as the experimental unit where appropriate). Descriptions of severity were included for the fetal defects observed.

Overall Quality Determination**Medium**

Study Citation:	Hazleton Labs, (1981). 1,3-Butadiene: Inhalation teratogenicity study in the rat (Final report).
Health Outcome(s) and Reported Health Effect(s):	Other (please specify below) (Clinical signs)-Non-organ-specific clinical signs (staining of fur, alopecia, lumps on the tail)-Renal/Kidney-Gross necropsy (hydronephrosis)-Lung/Respiratory-Gross necropsy (dark pink lungs)
Duration and Exposure Route:	Inhalation-Gas-Duration: Reproductive/Developmental-1-F0 - gestation (GD 6-15)
Species:	Rat-Sprague-Dawley - [rat]-Female
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	62371

Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	Medium	Quantitative data for all endpoints and exposure groups were provided. Summary tables for continuous data did not include measures of variance or an "N" to indicate sample size; however, individual animal data for all endpoints were provided in appendices. Statistical methods were clearly described and were appropriate for the datasets (the litter was used as the experimental unit where appropriate). Descriptions of severity were included for the fetal defects observed.
Domain 2: Selection and Performance			
	Metric 2: Allocation	Medium	Pregnant dams were allocated into exposure groups according to body weight. This was not combined with any other randomization procedure.
	Metric 3: Observational Bias / Blinding Changes	Medium	Blinding was not specified for clinical signs or gross necropsy.
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	Low	The study included air-only chamber controls. A positive control group was also included to demonstrate the sensitivity of the animal strain used; however, positive controls are generally not required for the study type. Respiratory rates were not reported for an inhalation study, but there is no conclusive data that the test substance is a respiratory irritant. Some fluctuations in temperature and humidity occurred that were outside of the acceptable range; however, these changes were attributed to inaccuracies of the instruments. The study authors noted several deviations between the controls used in this study and background/historical controls from the same laboratory. For example, control fetuses in this study were smaller (mean fetal weight and crown/rump length) than normal, and control animals showed low incidences of wavy ribs. This was considered to be unusual as incidences of wavy ribs are rarely found (1 incidence in 3,228 historical controls). These confounding factors make it difficult to interpret the study results. The authors opted to dismiss some statistically significant effects, attributing them to the noted differences in the animals used compared to normal.
Domain 4: Selective Reporting and Attrition			
	Metric 5: Selective Reporting and Attrition	High	Quantitative data for all endpoints and exposure groups were provided. There is no indication of selective reporting. All animals were healthy at the start of the exposure period. There is no information to suggest the presence of animal attrition.
Domain 5: Exposure Methods Sensitivity			

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Study Citation:	Hazleton Labs, (1981). 1,3-Butadiene: Inhalation teratogenicity study in the rat (Final report).
Health Outcome(s) and Reported Health Effect(s):	Other (please specify below) (Clinical signs)-Non-organ-specific clinical signs (staining of fur, alopecia, lumps on the tail)-Renal/Kidney-Gross necropsy (hydronephrosis)-Lung/Respiratory-Gross necropsy (dark pink lungs)
Duration and Exposure Route:	Inhalation-Gas-Duration: Reproductive/Developmental-1-F0 - gestation (GD 6-15)
Species:	Rat-Sprague-Dawley - [rat]-Female
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	62371

Domain	Metric	Rating	Comments
Metric 6:	Chemical administration and characterization	Low	The test substance was identified as 1,3-butadiene and was supplied by the study sponsor. The test substance was analyzed by the sponsor before sending, and samples were collected during and after the study period for additional analysis. The purity of the test substance was not explicitly reported. However, the analysis data provided reports concentrations of all impurities, so a general idea of purity can be determined. Samples were also analyzed for the presence of the 4-vinyl-1-cyclohexane dimer and the butadiene inhibitor (tertiary butyl-catechol)concentrations; concentrations fell within acceptable ranges. Details of atmosphere generation and the exposure chambers were provided. The process of volatilization was described; however, the study referred to the test substance as both a vapor and a gas seemingly interchangeably. Storage details were provided. The exposure atmospheres were monitored continuously for test substance concentration via GC. The analytical mean of chamber concentrations was provided. The inhalation route was justified by the study authors. Animals were exposed whole-body via inhalation in a dynamic chamber. The number of air changes (7.5-9.0 changes/hour) was lower than preferred (10/hr), which warrants a score of LOW; the flow rate was reported.
Metric 7:	Exposure timing, frequency, and duration	Medium	Animals were exposed for 6 hrs/day, from GD 6-15, which may not include the window of sensitivity for the endpoints evaluated. Exposure should begin on GD 5 to measure the effects on implantation and continue through GD 19 to measure skeletal effects. The exposure administration was consistent across groups.

Domain 6: Outcome Measures and Results Display

Metric 8:	Endpoint sensitivity and specificity	Medium	The study did not cite a specific guideline but was generally consistent with an OECD 414 prenatal developmental toxicity study which includes observations of clinical signs and gross necropsy. On their own, these measures are not sensitive for determining organ-specific toxicity, but the inclusion of clinical signs and gross necropsy is required in the OECD 414 TG. This study did not specify adherence to a guideline but is generally consistent with OECD 414. The exposure groups and spacing were set by the sponsors and justified. The test model was appropriate and justified by the study authors; susceptibility was demonstrated through the use of a positive control. The methods were adequately described and sampling was adequate to allow for statistical analysis.
Metric 9:	Results presentation	High	Quantitative data for all endpoints and exposure groups were provided. Individual animal data for all endpoints were provided in appendices. Statistical methods were clearly described and were appropriate for the datasets. Descriptions of severity were included where appropriate.

Overall Quality Determination

Medium

Study Citation:	PNL., Battelle (1987). Inhalation developmental toxicology studies: Teratology study of 1,3-butadiene in mice.		
Health Outcome(s) and Reported	Nutritional/Metabolic-Maternal body weight, Maternal weight gain (pre and post-gestation)-Mortality-Dam mortality		
Health Effect(s):			
Duration and Exposure Route:	Inhalation-Gas-Duration: Reproductive/Developmental-1-F0 - gestation (GD6-15)		
Species:	Mouse-CD-1 - [mouse]-Female		
Chemical:	1,3-Butadiene- Parent compound		
HERO ID:	62351		
Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
Metric 1: Reporting Quality		Medium	All critical and most important information were reported. Reported information included details of the test material (name, source, and purity); test model (species, strain, sex, source, initial body weights, and age); and animal husbandry (cage types, food and water availability, temperature, humidity, animals per cage). Exposure details, experimental methods, and quantitative results for all of the endpoints specified were reported. Lighting (light/dark cycle), and parity were not reported; animals were 7-8 weeks of age.
Domain 2: Selection and Performance			
Metric 2: Allocation		High	Pregnant dams were randomly assigned to groups using a computer-assisted randomization program and animals were normalized for body weight.
Metric 3: Observational Bias / Blinding Changes		Medium	Blinding was not specified; however, the endpoints were not subjective (e.g., mortality), were simple measures (e.g., body weights), or not required (initial histopathology)
Domain 3: Confounding / Variable Control			
Metric 4: Confounding / Variable Control		Medium	Concurrent air-only controls were included. Control mice showed a higher incidence of early resorptions than animals at the mid-dose. The authors did not specify whether the incidences in controls were outside of the expected range. The number of pregnant mice was low (60%), but there were no differences among treatment groups. Respiratory rates were not measured in an inhalation study; however, the test substance is not a known respiratory irritant in laboratory animals. Some variance in the chamber humidity levels was noted, with several occurrences of values dropping below the lower operating limit of 40% recorded in the control and high exposure groups. It is unclear if this contributed to the 3 high-exposure deaths attributed to dehydration.
Domain 4: Selective Reporting and Attrition			
Metric 5: Selective Reporting and Attrition		High	Mortalities were reported. three animals in the high exposure group died and the cause of death was associated with dehydration. There were no other indications of attrition. All animals were accounted for in the data tables, and there is no evidence of selective reporting.
Domain 5: Exposure Methods Sensitivity			

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Study Citation:	PNL., Battelle (1987). Inhalation developmental toxicology studies: Teratology study of 1,3-butadiene in mice.
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Maternal body weight, Maternal weight gain (pre and post-gestation)-Mortality-Dam mortality
Duration and Exposure Route:	Inhalation-Gas-Duration: Reproductive/Developmental-1-F0 - gestation (GD6-15)
Species:	Mouse-CD-1 - [mouse]-Female
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	62351

Domain	Metric	Rating	Comments
Metric 6:	Chemical administration and characterization	Medium	The test material was obtained from Phillips Chemical Company as a single batch and was characterized by the Midwest Research Institute. The performing laboratory also conducted a separate analysis and confirmed a purity of 99.88%. The 4-vinyl-1-cyclohexene dimer was also detected at 0.11%. The test material was stored at 72 degrees F and care was taken to minimize formation of and exposure to the dimer. The mean measured dimer concentration was 338 ppm. Chamber temperature and humidity levels were specified. Concentrations of the test material in the exposure chambers were monitored using GC. Animals were exposed whole-body in a dynamic flow chamber; however, the number of air changes/hour was not specified. The methods of atmosphere generation were described and appropriate. Concentrations were monitored using GC and were the same as the target values.
Metric 7:	Exposure timing, frequency, and duration	Low	Pregnant dams were exposed 6 hrs/day from GD 6-15. Exposures were consistent across groups. The study did not specify adherence to a guideline; however, the study intended to measure skeletal effects, which should include exposures through GD 19.

Domain 6: Outcome Measures and Results Display

Metric 8:	Endpoint sensitivity and specificity	High	The endpoints measured were generally consistent with those specified for similar study types (OECD TG 414), and were sensitive for the outcomes of interest. Animals were observed twice daily for mortality and morbidity. The authors justified the animal model and concentrations of exposure used.
Metric 9:	Results presentation	High	Individual animal data were provided. Summary tables reported means \pm SE, and the sample sizes were specified. Statistical methods were described and were appropriate for the datasets.

Overall Quality Determination

Medium

Study Citation:	PNL., Battelle (1987). Inhalation developmental toxicology studies: Teratology study of 1,3-butadiene in mice.		
Health Outcome(s) and Reported Health Effect(s):	Other (please specify below) (Clinical signs)-dehydration		
Duration and Exposure Route:	Inhalation-Gas-Duration: Reproductive/Developmental-1-F0 - gestation (GD6-15)		
Species:	Mouse-CD-1 - [mouse]-Female		
Chemical:	1,3-Butadiene- Parent compound		
HERO ID:	62351		
Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
Metric 1: Reporting Quality		Medium	All critical and most important information were reported. Reported information included details of the test material (name, source, and purity); test model (species, strain, sex, source, initial body weights, and age); and animal husbandry (cage types, food and water availability, temperature, humidity, animals per cage). Exposure details, experimental methods, and quantitative results for all of the endpoints specified were reported. Lighting (light/dark cycle), and parity were not reported; animals were 7-8 weeks of age.
Domain 2: Selection and Performance			
Metric 2: Allocation		High	Pregnant dams were randomly assigned to groups using a computer-assisted randomization program and animals were normalized for body weight.
Metric 3: Observational Bias / Blinding Changes		Medium	Blinding was not specified; however, the endpoints were not subjective (e.g., mortality), were simple measures (e.g., body weights), or not required (initial histopathology)
Domain 3: Confounding / Variable Control			
Metric 4: Confounding / Variable Control		Medium	Concurrent air-only controls were included. Control mice showed a higher incidence of early resorptions than animals at the mid-dose. The authors did not specify whether the incidences in controls were outside of the expected range. The number of pregnant mice was low (60%), but there were no differences among treatment groups. Respiratory rates were not measured in an inhalation study; however, the test substance is not a known respiratory irritant in laboratory animals. Some variance in the chamber humidity levels was noted, with several occurrences of values dropping below the lower operating limit of 40% recorded in the control and high exposure groups. It is unclear if this contributed to the 3 high-exposure deaths attributed to dehydration.
Domain 4: Selective Reporting and Attrition			
Metric 5: Selective Reporting and Attrition		High	Mortalities were reported. three animals in the high exposure group died and the cause of death was associated with dehydration. There were no other indications of attrition. All animals were accounted for in the data tables, and there is no evidence of selective reporting.
Domain 5: Exposure Methods Sensitivity			

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Study Citation:	PNL., Battelle (1987). Inhalation developmental toxicology studies: Teratology study of 1,3-butadiene in mice.
Health Outcome(s) and Reported Health Effect(s):	Other (please specify below) (Clinical signs)-dehydration
Duration and Exposure Route:	Inhalation-Gas-Duration: Reproductive/Developmental-1-F0 - gestation (GD6-15)
Species:	Mouse-CD-1 - [mouse]-Female
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	62351

Domain	Metric	Rating	Comments
Metric 6:	Chemical administration and characterization	Medium	The test material was obtained from Phillips Chemical Company as a single batch and was characterized by the Midwest Research Institute. The performing laboratory also conducted a separate analysis and confirmed a purity of 99.88%. The 4-vinyl-1-cyclohexene dimer was also detected at 0.11%. The test material was stored at 72 degrees F and care was taken to minimize formation of and exposure to the dimer. The mean measured dimer concentration was 338 ppm. Chamber temperature and humidity levels were specified. Concentrations of the test material in the exposure chambers were monitored using GC. Animals were exposed whole-body in a dynamic flow chamber; however, the number of air changes/hour was not specified. The methods of atmosphere generation were described and appropriate. Concentrations were monitored using GC and were the same as the target values.
Metric 7:	Exposure timing, frequency, and duration	Low	Pregnant dams were exposed 6 hrs/day from GD 6-15. Exposures were consistent across groups. The study did not specify adherence to a guideline; however, the study intended to measure skeletal effects, which should include exposures through GD 19.

Domain 6: Outcome Measures and Results Display

Metric 8:	Endpoint sensitivity and specificity	Medium	The endpoints measured were generally consistent with those specified for similar study types (OECD TG 414). Animals were observed twice daily for signs of toxicity; however, no additional details were provided (e.g., no specification of cage-side only or detailed clinical observations). The authors justified the animal model and concentrations of exposure used.
Metric 9:	Results presentation	Medium	Negative findings were qualitatively described in the text.

Overall Quality Determination

Medium

Study Citation:	PNL., Battelle (1987). Inhalation developmental toxicology studies: Teratology study of 1,3-butadiene in mice.		
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Gravid uterine weights, placenta weight, number of implantation sites, early and late resorptions, fetal sex and weight. Gross, visceral, and skeletal examinations, fetal lens opacity, and microscopic examination of fetal eyes.		
Duration and Exposure Route:	Inhalation-Gas-Duration: Reproductive/Developmental-1-F0 - gestation (GD6-15)		
Species:	Mouse-CD-1 - [mouse]-Female		
Chemical:	1,3-Butadiene- Parent compound		
HERO ID:	62351		
Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
Metric 1: Reporting Quality	Medium	All critical and most important information were reported. Reported information included details of the test material (name, source, and purity); test model (species, strain, sex, source, initial body weights, and age); and animal husbandry (cage types, food and water availability, temperature, humidity, animals per cage). Exposure details, experimental methods, and quantitative results for all of the endpoints specified were reported. Lighting (light/dark cycle), and parity were not reported; animals were 7-8 weeks of age.	
Domain 2: Selection and Performance			
Metric 2: Allocation	High	Pregnant dams were randomly assigned to groups using a computer-assisted randomization program and animals were normalized for body weight.	
Metric 3: Observational Bias / Blinding Changes	Medium	Blinding was not specified; however, the endpoints were not subjective (e.g., mortality), were simple measures (e.g., body weights), or not required (initial histopathology)	
Domain 3: Confounding / Variable Control			
Metric 4: Confounding / Variable Control	Medium	Concurrent air-only controls were included. Control mice showed a higher incidence of early resorptions than animals at the mid-dose. The authors did not specify whether the incidences in controls were outside of the expected range. The number of pregnant mice was low (60%), but there were no differences among treatment groups. Respiratory rates were not measured in an inhalation study; however, the test substance is not a known respiratory irritant in laboratory animals. Some variance in the chamber humidity levels was noted, with several occurrences of values dropping below the lower operating limit of 40% recorded in the control and high exposure groups. It is unclear if this contributed to the 3 high-exposure deaths attributed to dehydration.	
Domain 4: Selective Reporting and Attrition			
Metric 5: Selective Reporting and Attrition	High	Mortalities were reported. three animals in the high exposure group died and the cause of death was associated with dehydration. There were no other indications of attrition. All animals were accounted for in the data tables, and there is no evidence of selective reporting.	
Domain 5: Exposure Methods Sensitivity			

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Study Citation:	PNL., Battelle (1987). Inhalation developmental toxicology studies: Teratology study of 1,3-butadiene in mice.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Gravid uterine weights, placenta weight, number of implantation sites, early and late resorptions, fetal sex and weight. Gross, visceral, and skeletal examinations, fetal lens opacity, and microscopic examination of fetal eyes.
Duration and Exposure Route:	Inhalation-Gas-Duration: Reproductive/Developmental-1-F0 - gestation (GD6-15)
Species:	Mouse-CD-1 - [mouse]-Female
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	62351

Domain	Metric	Rating	Comments
Metric 6:	Chemical administration and characterization	Medium	The test material was obtained from Phillips Chemical Company as a single batch and was characterized by the Midwest Research Institute. The performing laboratory also conducted a separate analysis and confirmed a purity of 99.88%. The 4-vinyl-1-cyclohexene dimer was also detected at 0.11%. The test material was stored at 72 degrees F and care was taken to minimize formation of and exposure to the dimer. The mean measured dimer concentration was 338 ppm. Chamber temperature and humidity levels were specified. Concentrations of the test material in the exposure chambers were monitored using GC. Animals were exposed whole-body in a dynamic flow chamber; however, the number of air changes/hour was not specified. The methods of atmosphere generation were described and appropriate. Concentrations were monitored using GC and were the same as the target values.
Metric 7:	Exposure timing, frequency, and duration	Low	Pregnant dams were exposed 6 hrs/day from GD 6-15. Exposures were consistent across groups. The study did not specify adherence to a guideline; however, the study intended to measure skeletal effects, which should include exposures through GD 19.

Domain 6: Outcome Measures and Results Display

Metric 8:	Endpoint sensitivity and specificity	Medium	The endpoints measured were generally consistent with those specified for similar study types (OECD TG 414), and were sensitive for the outcomes of interest. Some treatment groups had fewer than 20 litters due to the low level of females that were actually pregnant. The authors justified the animal model and concentrations of exposure used. The authors justified the animal model and concentrations of exposure used.
Metric 9:	Results presentation	High	Individual animal data were provided. Summary tables reported means \pm SE, and the sample sizes were specified. The litter was used as the experimental unit where appropriate.

Overall Quality Determination**Medium**

Study Citation:	PNL., Battelle (1987). Inhalation developmental toxicology studies of 1,3-butadiene in the rat.		
Health Outcome(s) and Reported	Reproductive/Developmental-Weight of gravid uterus, placental weight, number of implantation sites, intrauterine mortality, placental weights, fetal observations (body weights, sex, lens opacity, examination of eyes, gross, visceral, and skeletal examinations)		
Health Effect(s):			
Duration and Exposure Route:	Inhalation-Gas-Duration: Reproductive/Developmental-F0 - gestation (GD 6-15)		
Species:	Rat-Sprague-Dawley - [rat]-Female		
Chemical:	1,3-Butadiene- Parent compound		
HERO ID:	94731		
Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
Metric 1:	Reporting Quality	Medium	All critical and most important information was reported. Sprague-Dawley rats (sex, source, age, initial body weights provided) were exposed whole body to 1,3-butadiene (source, purity, composition reported). Details of caging, the inhalation chamber, the number of animals per group, and atmosphere generation were described. Animal husbandry (food and water availability, temperature, humidity, and animals per cage) details were reported. Outcome assessment methods and results for all outcomes were reported. Missing information included female parity (although animals were 7-8 weeks old), and the photoperiod.
Domain 2: Selection and Performance			
Metric 2:	Allocation	High	Females were allocated into groups using a computer-assisted randomization program using body weights as a blocking factor.
Metric 3:	Observational Bias / Blinding Changes	Medium	Blinding was not specified; however, blinding is not required for the reproductive/endpoints evaluated in a standard teratogenicity study
Domain 3: Confounding / Variable Control			
Metric 4:	Confounding / Variable Control	Medium	The study used an appropriate (air only) negative control. The negative control responses were acceptable. A positive control is not required for this study type. Reflex bradypnea was not monitored in an inhalation study; however, the test chemical is not considered to be a respiratory irritant in animals. There were no significant changes in body weights suggestive of differences in food or water intake. No other potentially confounding variables were observed.
Domain 4: Selective Reporting and Attrition			
Metric 5:	Selective Reporting and Attrition	High	No animals in the study died. Data were reported for all animals that were pregnant, and individual animal data were provided. Data from 1 animal in the high-exposure group that only had one implantation was excluded from statistical analysis. The authors considered this animal to be an outlier. Although it was excluded, the authors provided a separate set of means for all of the endpoints specified in the table that included this animal to allow for any independent analysis. There is no indication of selective reporting.
Domain 5: Exposure Methods Sensitivity			

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Study Citation:	PNL., Battelle (1987). Inhalation developmental toxicology studies of 1,3-butadiene in the rat.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Weight of gravid uterus, placental weight, number of implantation sites, intrauterine mortality, placental weights, fetal observations (body weights, sex, lens opacity, examination of eyes, gross, visceral, and skeletal examinations)
Duration and Exposure Route:	Inhalation-Gas-Duration: Reproductive/Developmental-F0 - gestation (GD 6-15)
Species:	Rat-Sprague-Dawley - [rat]-Female
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	94731

Domain	Metric	Rating	Comments
Metric 6:	Chemical administration and characterization	Medium	There were no concerns about the test substance identity. 1,3-butadiene was procured from Phillips Chemical Company. The lot and batch number was provided, and the purity was 99.88%. It was analyzed by the performing laboratory using GC. All contaminants were identified. Storage details were provided and were appropriate for a volatile chemical. Care was also taken to prevent or minimize temperature-induced dimer formation. Exposure chamber and atmosphere generation methods were described in detail. Animals were exposed whole body in dynamic chambers; however, the number of air changes per hour was not specified. Exposure concentrations were analytically monitored using GC-FID. Target and measured values were reported. Concentrations of the dimer were also monitored.
Metric 7:	Exposure timing, frequency, and duration	Low	The duration of exposure (GD 6-15) was not sensitive for assessing effects on implantation (occurs on GD5 in rats), or for evaluating skeletal effects (exposure should extend through GD19), and these endpoints were included in the study. This may bias the results towards the null.

Domain 6: Outcome Measures and Results Display

Metric 8:	Endpoint sensitivity and specificity	High	The study generally assessed the endpoints described in a prenatal developmental toxicity study (OECD TG 414), and the outcome assessment methods were sensitive to the outcomes of interest. The authors provided justification for the species/strain used and the exposure concentrations/spacing were selected based on observations from other studies. However, the study conditions were not sufficient for identifying a LOAEL; although this may be influenced by an insufficient exposure duration rather than insufficient concentrations or spacing. The sample sizes were reported and were sufficient for statistical analysis.
Metric 9:	Results presentation	High	The statistical methods did not explicitly report that the litter was used as the experimental unit, but this was clear when viewing the data tables. Data were presented as means \pm SE where appropriate and individual animal data were provided in the appendices.

Overall Quality Determination

Medium

Study Citation:	PNL., Battelle (1987). Inhalation developmental toxicology studies of 1,3-butadiene in the rat.
Health Outcome(s) and Reported Health Effect(s):	Mortality-Maternal mortality-Nutritional/Metabolic-Maternal body weights; weight gain (during gestation); extragestational weight gain
Duration and Exposure Route:	Inhalation-Gas-Duration: Reproductive/Developmental-F0 - gestation (GD 6-15)
Species:	Rat-Sprague-Dawley - [rat]-Female
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	94731

Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	Medium	All critical and most important information was reported. Sprague-Dawley rats (sex, source, age, initial body weights provided) were exposed whole body to 1,3-butadiene (source, purity, composition reported). Details of caging, the inhalation chamber, the number of animals per group, and atmosphere generation were described. Animal husbandry (food and water availability, temperature, humidity, and animals per cage) details were reported. Outcome assessment methods and results for all outcomes were reported. Missing information included female parity (although animals were 7-8 weeks old), and the photoperiod.
Domain 2: Selection and Performance			
	Metric 2: Allocation	High	Females were allocated into groups using a computer-assisted randomization program using body weights as a blocking factor.
	Metric 3: Observational Bias / Blinding Changes	Medium	Blinding was not specified; however, blinding is not required for the specified outcomes (mortality and body weights)
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	Medium	The study used an appropriate (air only) negative control. The negative control responses were acceptable. A positive control is not required for this study type. Reflex bradypnea was not monitored in an inhalation study; however, the test chemical is not considered to be a respiratory irritant in animals. There were no significant changes in body weights suggestive of differences in food or water intake. No other potentially confounding variables were observed.
Domain 4: Selective Reporting and Attrition			
	Metric 5: Selective Reporting and Attrition	High	No animals in the study died. Data were reported for all animals that were pregnant, and individual animal data were provided. Data from 1 animal in the high-exposure group that only had one implantation was excluded from statistical analysis. The authors considered this animal to be an outlier. Although it was excluded, the authors provided a separate set of means for all of the endpoints specified in the table that included this animal to allow for any independent analysis. There is no indication of selective reporting.
Domain 5: Exposure Methods Sensitivity			

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Study Citation:	PNL., Battelle (1987). Inhalation developmental toxicology studies of 1,3-butadiene in the rat.
Health Outcome(s) and Reported Health Effect(s):	Mortality-Maternal mortality-Nutritional/Metabolic-Maternal body weights; weight gain (during gestation); extragestational weight gain
Duration and Exposure Route:	Inhalation-Gas-Duration: Reproductive/Developmental-F0 - gestation (GD 6-15)
Species:	Rat-Sprague-Dawley - [rat]-Female
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	94731

Domain	Metric	Rating	Comments
Metric 6:	Chemical administration and characterization	Medium	There were no concerns about the test substance identity. 1,3-butadiene was procured from Phillips Chemical Company. The lot and batch number was provided, and the purity was 99.88%. It was analyzed by the performing laboratory using GC. All contaminants were identified. Storage details were provided and were appropriate for a volatile chemical. Care was also taken to prevent or minimize temperature-induced dimer formation. Exposure chamber and atmosphere generation methods were described in detail. Animals were exposed whole body in dynamic chambers; however, the number of air changes per hour was not specified. Exposure concentrations were analytically monitored using GC-FID. Target and measured values were reported. Concentrations of the dimer were also monitored.
Metric 7:	Exposure timing, frequency, and duration	High	The exposure timing, frequency, and duration (6hrs/day from GDs 5-15) were sufficient for evaluating the outcomes of interest (mortality and body weights).

Domain 6: Outcome Measures and Results Display

Metric 8:	Endpoint sensitivity and specificity	High	The study generally assessed the endpoints described in a prenatal developmental toxicity study (OECD TG 414), and the outcome assessment methods were sensitive to the outcomes of interest. The authors provided justification for the species/strain used and the exposure concentrations/spacing were selected based on observations from other studies. However, the study conditions were not sufficient for identifying a LOAEL; although this may be influenced by an insufficient exposure duration rather than insufficient concentrations or spacing. The sample sizes were reported and were sufficient for statistical analysis.
Metric 9:	Results presentation	High	The statistical methods were adequately described. A qualitative statement was made that no animals died. Data for body weights were presented as means \pm SE and individual animal data were provided in the appendices.

Overall Quality Determination**High**

Study Citation:	PNL,, Battelle (1987). Inhalation developmental toxicology studies of 1,3-butadiene in the rat.
Health Outcome(s) and Reported Health Effect(s):	Other (please specify below) (Clinical signs)-Maternal clinical signs of toxicity
Duration and Exposure Route:	Inhalation-Gas-Duration: Reproductive/Developmental-F0 - gestation (GD 6-15)
Species:	Rat-Sprague-Dawley - [rat]-Female
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	94731

Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	Medium	All critical and most important information was reported. Sprague-Dawley rats (sex, source, age, initial body weights provided) were exposed whole body to 1,3-butadiene (source, purity, composition reported). Details of caging, the inhalation chamber, the number of animals per group, and atmosphere generation were described. Animal husbandry (food and water availability, temperature, humidity, and animals per cage) details were reported. Outcome assessment methods and results for all outcomes were reported. Missing information included female parity (although animals were 7-8 weeks old), and the photoperiod.
Domain 2: Selection and Performance			
	Metric 2: Allocation	High	Females were allocated into groups using a computer-assisted randomization program using body weights as a blocking factor.
	Metric 3: Observational Bias / Blinding Changes	Medium	Blinding was not specified for clinical signs
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	Medium	The study used an appropriate (air only) negative control. The negative control responses were acceptable. A positive control is not required for this study type. Reflex bradypnea was not monitored in an inhalation study; however, the test chemical is not considered to be a respiratory irritant in animals. There were no significant changes in body weights suggestive of differences in food or water intake. No other potentially confounding variables were observed.
Domain 4: Selective Reporting and Attrition			
	Metric 5: Selective Reporting and Attrition	High	No animals in the study died. Data were reported for all animals that were pregnant, and individual animal data were provided. Data from 1 animal in the high-exposure group that only had one implantation was excluded from statistical analysis. The authors considered this animal to be an outlier. Although it was excluded, the authors provided a separate set of means for all of the endpoints specified in the table that included this animal to allow for any independent analysis. There is no indication of selective reporting.
Domain 5: Exposure Methods Sensitivity			

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Study Citation: PNL., Battelle (1987). Inhalation developmental toxicology studies of 1,3-butadiene in the rat.
Health Outcome(s) and Reported Health Effect(s): Other (please specify below) (Clinical signs)-Maternal clinical signs of toxicity
Duration and Exposure Route: Inhalation-Gas-Duration: Reproductive/Developmental-F0 - gestation (GD 6-15)
Species: Rat-Sprague-Dawley - [rat]-Female
Chemical: 1,3-Butadiene- Parent compound
HERO ID: 94731

Domain	Metric	Rating	Comments
	Metric 6: Chemical administration and characterization	Medium	There were no concerns about the test substance identity. 1,3-butadiene was procured from Phillips Chemical Company. The lot and batch number was provided, and the purity was 99.88%. It was analyzed by the performing laboratory using GC. All contaminants were identified. Storage details were provided and were appropriate for a volatile chemical. Care was also taken to prevent or minimize temperature-induced dimer formation. Exposure chamber and atmosphere generation methods were described in detail. Animals were exposed whole body in dynamic chambers; however, the number of air changes per hour was not specified. Exposure concentrations were analytically monitored using GC-FID. Target and measured values were reported. Concentrations of the dimer were also monitored.
	Metric 7: Exposure timing, frequency, and duration	Low	The duration of exposure (GD 6-15) was not sensitive for assessing effects on implantation (occurs on GD5 in rats), or for evaluating skeletal effects (exposure should extend through GD19), and these endpoints were included in the study. This may bias the results towards the null.

Domain 6: Outcome Measures and Results Display

Metric 8: Endpoint sensitivity and specificity	Low	The study generally assessed the endpoints described in a prenatal developmental toxicity study (OECD TG 414). Animals were observed for clinical signs twice daily; clinical signs in general are not considered to be a sensitive outcome for specific organ/system toxicity. The authors provided justification for the species/strain used and the exposure concentrations/spacing were selected based on observations from other studies. However, the study conditions were not sufficient for identifying a LOAEL; although this may be influenced by an insufficient exposure duration rather than insufficient concentrations or spacing. The sample sizes were reported and were sufficient for statistical analysis.
Metric 9: Results presentation	Uninformative	The statistical methods were generally described, although it is not clear what methods were applied to clinical observations if any. A qualitative statement reported that no clinical signs of toxicity were observed in the low and mid-exposure groups. Results for the high-exposure group were not reported. The lack of sufficient reporting precludes the ability to evaluate this outcome of interest.

Overall Quality Determination

Uninformative

Study Citation:	WIL Research, (2003). An inhalation reproduction/developmental toxicity screening study of 1,3-butadiene in rats.		
Health Outcome(s) and Reported	Nutritional/Metabolic-Body weight, body weight gain, food consumption, food efficiency		
Health Effect(s):			
Duration and Exposure Route:	Inhalation-Vapor-Duration: Reproductive/Developmental-2-F0- pre mating (14 Days)-F0- mating (During 14-day mating period)-F0 - gestation (Through-out gestation until GD 20)-F0- lactation (From LD 5 until the day prior to euthanasia for a total of 60 to 70 days of exposure)-F1- post-natal (PND 21-27 or 28-34)-F0- pre mating (14 Days)-F0- mating (From LD 5 until the day prior to euthanasia for a total of 60 to 70 days of exposure)-F1- post-natal (PND 21-27 or 28-34)		
Species:	Rat-Sprague-Dawley - [rat]-Both		
Chemical:	1,3-Butadiene- Parent compound		
HERO ID:	10367501		
Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
Metric 1:	Reporting Quality	Medium	All critical information is reported. Some important information is not reported, including parity of animals used in the study and the number of animals per cage throughout the study (e.g., for F0 male animals following pairing, the number of animals per cage is not stated).
Domain 2: Selection and Performance			
Metric 2:	Allocation	High	The allocation method for assignment of animals to groups was based on stratified body weights with computer-selected randomization.
Metric 3:	Observational Bias / Blinding Changes	Medium	Measures to reduce observational bias were not reported; however, this is not expected to significantly impact the study because the endpoints evaluated are not subjective.
Domain 3: Confounding / Variable Control			
Metric 4:	Confounding / Variable Control	Medium	There is some concern that confounding factors that may modify the results were uncontrolled due to incomplete reporting of animal husbandry (e.g., parity of animals used in the study), but likely not a significant impact on results.
Domain 4: Selective Reporting and Attrition			
Metric 5:	Selective Reporting and Attrition	Medium	Most animals are accounted for in the results presented. Some data tables shown in HERO ID 10367501 (e.g., parental male body weights; parental female body weights during gestation and lactation; parental female food consumption during lactation) provide results for a fewer number of females than original treatment group sizes of 12. For the body weight tables, for example, this is due to one male mortality at 6000 ppm; and non-gravid females (e.g., 2 in the control, 1 at 6000 ppm); or total litter loss (e.g., 1 in the control group, 2 at 1500 ppm). A protocol deviation (HERO ID 10367501, Section 5.1.3, report p. 64 of 858) notes that food weights were inadvertently not collected for lactation day 28 females. However, the reason for reporting data for a portion of the groups (e.g., for example, 9, 8, 7, and 8 animals in the respective 0, 300, 1500, and 6000 ppm groups for LD 28 food consumption data; for example, Tables 19, 69, and 70) is not fully explained by this protocol deviation or other reported findings mentioned above. This is not expected to impact the study results or conclusions because there were no effects on body weight or food consumption for this timepoint.

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Study Citation:	WIL Research, (2003). An inhalation reproduction/developmental toxicity screening study of 1,3-butadiene in rats.
Health Outcome(s) and Reported Health Effect(s):	Nutritional/Metabolic-Body weight, body weight gain, food consumption, food efficiency
Duration and Exposure Route:	Inhalation-Vapor-Duration: Reproductive/Developmental-2-F0- pre mating (14 Days)-F0- mating (During 14-day mating period)-F0 - gestation (Throughout gestation until GD 20)-F0- lactation (From LD 5 until the day prior to euthanasia for a total of 60 to 70 days of exposure)-F1- post-natal (PND 21-27 or 28-34)-F0- pre mating (14 Days)-F0- mating (From LD 5 until the day prior to euthanasia for a total of 60 to 70 days of exposure)-F1- post-natal (PND 21-27 or 28-34)
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	10367501

Domain	Metric	Rating	Comments
Domain 5: Exposure Methods Sensitivity			
	Metric 6: Chemical administration and characterization	High	Inhalation exposure administration methods were adequately characterized in the study reports. The study used dynamic whole-body chambers with 12-15 air changes per hour. Test concentrations were monitored during the inhalation exposures. The inhalation route and exposure method were considered appropriate for the study type and outcomes evaluated. Purity and stability of the test substance were determined in an independent study (results are reported in Appendix C of HERO ID 10367501).
	Metric 7: Exposure timing, frequency, and duration	High	The timing, duration, and frequency of the exposure appear to be appropriate for the study type and the outcomes evaluated.
Domain 6: Outcome Measures and Results Display			
	Metric 8: Endpoint sensitivity and specificity	High	The procedures were sensitive and specific for the outcomes measured and endpoints of interest.
	Metric 9: Results presentation	High	Results presentation appears to be appropriate for the study type and endpoints evaluated for data that are reported. Mean values for each group are provided with variance and incidence data are reported by group. Individual data are reported in appended sections.

Overall Quality Determination	High

Study Citation:	WIL Research, (2003). An inhalation reproduction/developmental toxicity screening study of 1,3-butadiene in rats.
Health Outcome(s) and Reported Health Effect(s):	Neurological/Behavioral-Clinical observations (presence of convulsions, tremors or abnormal movements, presence of posture and gait abnormalities, the presence of any unusual or abnormal behaviors and any repetitive actions); macroscopic examination of the cranial cavity, brain, and spinal cord; brain weight-Lung/Respiratory-Appearance of mucous membranes and respiratory system/respiration; macroscopic examination of the thoracic cavity-Other (please specify below) (Clinical signs)-Appearance (skin, fur), salivation, lacrimation, presence or absence of urination and/or defecation-Ocular/Sensory-Pupil size, degree of palpebral closure
Duration and Exposure Route:	Inhalation-Vapor-Duration: Reproductive/Developmental-2-F0- pre mating (14 Days)-F0- mating (During 14-day mating period)-F0 - gestation (Throughout gestation until GD 20)-F0- lactation (From LD 5 until the day prior to euthanasia for a total of 60 to 70 days of exposure)-F1- post-natal (PND 21-27 or 28-34)-F0- pre mating (14 Days)-F0- mating (From LD 5 until the day prior to euthanasia for a total of 60 to 70 days of exposure)-F1- post-natal (PND 21-27 or 28-34)
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	10367501

Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	Medium	All critical information is reported. Some important information is not reported, including parity of animals used in the study and the number of animals per cage throughout the study (e.g., for F0 male animals following pairing, the number of animals per cage is not stated).
Domain 2: Selection and Performance			
	Metric 2: Allocation	High	The allocation method for assignment of animals to groups was based on stratified body weights with computer-selected randomization.
	Metric 3: Observational Bias / Blinding Changes	Low	Measures to reduce observational bias were not reported and some of the endpoints for the outcomes in this evaluation are subjective; therefore, a rating of Low was selected.
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	Medium	There is some concern that confounding factors that may modify the results were uncontrolled due to incomplete reporting of animal husbandry (e.g., parity of animals used in the study), but likely not a significant impact on results.
Domain 4: Selective Reporting and Attrition			
	Metric 5: Selective Reporting and Attrition	High	All animals are accounted for in the presented results and there were no unexplained omissions or attrition.
Domain 5: Exposure Methods Sensitivity			
	Metric 6: Chemical administration and characterization	High	Inhalation exposure administration methods were adequately characterized in the study reports. The study used dynamic whole-body chambers with 12-15 air changes per hour. Test concentrations were monitored during the inhalation exposures. The inhalation route and exposure method were considered appropriate for the study type and outcomes evaluated. Purity and stability of the test substance were determined in an independent study (results are reported in Appendix C of HERO ID 10367501).
	Metric 7: Exposure timing, frequency, and duration	High	The timing, duration, and frequency of the exposure appear to be appropriate for the study type and the outcomes evaluated.
Domain 6: Outcome Measures and Results Display			

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Study Citation:	WIL Research, (2003). An inhalation reproduction/developmental toxicity screening study of 1,3-butadiene in rats.
Health Outcome(s) and Reported Health Effect(s):	Neurological/Behavioral-Clinical observations (presence of convulsions, tremors or abnormal movements, presence of posture and gait abnormalities, the presence of any unusual or abnormal behaviors and any repetitive actions); macroscopic examination of the cranial cavity, brain, and spinal cord; brain weight-Lung/Respiratory-Appearance of mucous membranes and respiratory system/respiration; macroscopic examination of the thoracic cavity-Other (please specify below) (Clinical signs)-Appearance (skin, fur), salivation, lacrimation, presence or absence of urination and/or defecation-Ocular/Sensory-Pupil size, degree of palpebral closure
Duration and Exposure Route:	Inhalation-Vapor-Duration: Reproductive/Developmental-2-F0- pre mating (14 Days)-F0- mating (During 14-day mating period)-F0 - gestation (Throughout gestation until GD 20)-F0- lactation (From LD 5 until the day prior to euthanasia for a total of 60 to 70 days of exposure)-F1- post-natal (PND 21-27 or 28-34)-F0- pre mating (14 Days)-F0- mating (From LD 5 until the day prior to euthanasia for a total of 60 to 70 days of exposure)-F1- post-natal (PND 21-27 or 28-34)
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	10367501

Domain	Metric	Rating	Comments
	Metric 8: Endpoint sensitivity and specificity	High	The procedures were sensitive and specific for the outcomes measured and endpoints of interest.
	Metric 9: Results presentation	High	Results presentation appears to be appropriate for the study type and endpoints evaluated for data that are reported. Mean values for each group are provided with variance and incidence data are reported by group. Individual data are reported in appended sections.

Overall Quality Determination **High**

Study Citation:	WIL Research, (2003). An inhalation reproduction/developmental toxicity screening study of 1,3-butadiene in rats.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Reproduction parameters: Male mating index; female mating index; male fertility index; female fertility index; parturition; gestation length; live litter size; spermatogenic endpoints (motility, morphology, spermatid count, sperm production rate); macroscopic examination of the mammary glands; histopathological examination of the ovaries, testes, and epididymides (right only; caput, corpus, and cauda); organ weights (epididymides [total and cauda], ovaries, prostate, seminal vesicles with coagulating glands [with accessory fluids], testes, and uterus with oviducts and cervix). Developmental parameters: offspring clinical observations (appearance, behavior); detailed physical examination; number born; sex at birth (% males/litter); live litter size (PND 0); postnatal survival; body weight; gross malformations; number of stillborn pups; number of live pups
Duration and Exposure Route:	Inhalation-Vapor-Duration: Reproductive/Developmental-2-F0- pre mating (14 Days)-F0- mating (During 14-day mating period)-F0 - gestation (Throughout gestation until GD 20)-F0- lactation (From LD 5 until the day prior to euthanasia for a total of 60 to 70 days of exposure)-F1- post-natal (PND 21-27 or 28-34)-F0- pre mating (14 Days)-F0- mating (From LD 5 until the day prior to euthanasia for a total of 60 to 70 days of exposure)-F1- post-natal (PND 21-27 or 28-34)
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	10367501

Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	Medium	All critical information is reported. Some important information is not reported, including parity of animals used in the study and the number of animals per cage throughout the study (e.g., for F0 male animals following pairing, the number of animals per cage is not stated).
Domain 2: Selection and Performance			
	Metric 2: Allocation	High	The allocation method for assignment of animals to groups was based on stratified body weights with computer-selected randomization.
	Metric 3: Observational Bias / Blinding Changes	Low	Measures to reduce observational bias were not reported and some of the endpoints for the outcomes in this evaluation (e.g., sperm parameters, such as morphology) may be subjective; therefore, a rating of Low was selected.
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	Low	There is some concern that confounding factors that may modify the results were uncontrolled due to incomplete reporting of animal husbandry (e.g., parity of animals used in the study). Concerns were identified related to control results for some reproductive endpoints. For fertility index, the control group value was lower than expected when compared to historical control data. The study authors provided the following explanation (on p. 41 of 858): "The control group fertility indices for males and females in this study (83.3%) were below the minimum values in the WIL historical control database for inhalation reproduction studies. The small sample size employed in this screening study caused these values to appear low based on only two non-gravid females. Nonetheless, the values in all of the test article exposure groups were higher than the control group values and were not statistically significant." Regarding recommended numbers of animals per group, this study contains the OECD-recommended number of animals, so that explanation is less convincing.
Domain 4: Selective Reporting and Attrition			
	Metric 5: Selective Reporting and Attrition	High	All animals are accounted for in the presented results and there were no unexplained omissions or attrition.

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Study Citation:	WIL Research, (2003). An inhalation reproduction/developmental toxicity screening study of 1,3-butadiene in rats.
Health Outcome(s) and Reported Health Effect(s):	Reproductive/Developmental-Reproduction parameters: Male mating index; female mating index; male fertility index; female fertility index; parturition; gestation length; live litter size; spermatogenic endpoints (motility, morphology, spermatid count, sperm production rate); macroscopic examination of the mammary glands; histopathological examination of the ovaries, testes, and epididymides (right only; caput, corpus, and cauda); organ weights (epididymides [total and cauda], ovaries, prostate, seminal vesicles with coagulating glands [with accessory fluids], testes, and uterus with oviducts and cervix). Developmental parameters: offspring clinical observations (appearance, behavior); detailed physical examination; number born; sex at birth (% males/litter); live litter size (PND 0); postnatal survival; body weight; gross malformations; number of stillborn pups; number of live pups
Duration and Exposure Route:	Inhalation-Vapor-Duration: Reproductive/Developmental-2-F0- premating (14 Days)-F0- mating (During 14-day mating period)-F0 - gestation (Throughout gestation until GD 20)-F0- lactation (From LD 5 until the day prior to euthanasia for a total of 60 to 70 days of exposure)-F1- post-natal (PND 21-27 or 28-34)-F0- premating (14 Days)-F0- mating (From LD 5 until the day prior to euthanasia for a total of 60 to 70 days of exposure)-F1- post-natal (PND 21-27 or 28-34)
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	10367501

Domain	Metric	Rating	Comments
Domain 5: Exposure Methods Sensitivity			
	Metric 6: Chemical administration and characterization	High	Inhalation exposure administration methods were adequately characterized in the study reports. The study used dynamic whole-body chambers with 12-15 air changes per hour. Test concentrations were monitored during the inhalation exposures. The inhalation route and exposure method were considered appropriate for the study type and outcomes evaluated. Purity and stability of the test substance were determined in an independent study (purity study results are reported in Appendix C of HERO ID 10367501).
	Metric 7: Exposure timing, frequency, and duration	High	The timing, duration, and frequency of the exposure appear to be appropriate for the study type and the outcomes evaluated.
Domain 6: Outcome Measures and Results Display			
	Metric 8: Endpoint sensitivity and specificity	High	The procedures were sensitive and specific for the outcomes measured and endpoints of interest.
	Metric 9: Results presentation	High	Results presentation appears to be appropriate for the study type and endpoints evaluated for data that are reported. Mean values for each group are provided with variance and incidence data are reported by group. Individual data are reported in appended sections.

Overall Quality Determination**Medium**

Study Citation:	WIL Research, (2003). An inhalation reproduction/developmental toxicity screening study of 1,3-butadiene in rats.
Health Outcome(s) and Reported Health Effect(s):	Mortality-Mortality-Immune/Hematological-Macroscopic examination of the lymph nodes-Thyroid-Macroscopic examination of the thyroid glands-Gastrointestinal-Macroscopic examination of the abdominal and pelvic cavities-Other (please specify below) (Endocrine organs)-Pituitary weight
Duration and Exposure Route:	Inhalation-Vapor-Duration: Reproductive/Developmental-2-F0- pre mating (14 Days)-F0- mating (During 14-day mating period)-F0 - gestation (Throughout gestation until GD 20)-F0- lactation (From LD 5 until the day prior to euthanasia for a total of 60 to 70 days of exposure)-F1- post-natal (PND 21-27 or 28-34)-F0- pre mating (14 Days)-F0- mating (From LD 5 until the day prior to euthanasia for a total of 60 to 70 days of exposure)-F1- post-natal (PND 21-27 or 28-34)
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	10367501

Domain	Metric	Rating	Comments
Domain 1: Reporting Quality			
	Metric 1: Reporting Quality	Medium	All critical information is reported. Some important information is not reported, including parity of animals used in the study and the number of animals per cage throughout the study (e.g., for F0 male animals following pairing, the number of animals per cage is not stated).
Domain 2: Selection and Performance			
	Metric 2: Allocation	High	The allocation method for assignment of animals to groups was based on stratified body weights with computer-selected randomization.
	Metric 3: Observational Bias / Blinding Changes	Medium	Measures to reduce observational bias were not reported; however, this is not expected to significantly impact the study because the endpoints evaluated are not subjective or were considered initial histopathology.
Domain 3: Confounding / Variable Control			
	Metric 4: Confounding / Variable Control	Medium	There is some concern that confounding factors that may modify the results were uncontrolled due to incomplete reporting of animal husbandry (e.g., parity of animals used in the study), but likely not a significant impact on results.
Domain 4: Selective Reporting and Attrition			
	Metric 5: Selective Reporting and Attrition	High	All animals are accounted for in the presented results and there were no unexplained omissions or attrition.
Domain 5: Exposure Methods Sensitivity			
	Metric 6: Chemical administration and characterization	High	Inhalation exposure administration methods were adequately characterized in the study reports. The study used dynamic whole-body chambers with 12-15 air changes per hour. Test concentrations were monitored during the inhalation exposures. The inhalation route and exposure method were considered appropriate for the study type and outcomes evaluated. Purity and stability of the test substance were determined in an independent study (results are reported in Appendix C of HERO ID 10367501).
	Metric 7: Exposure timing, frequency, and duration	High	The timing, duration, and frequency of the exposure appear to be appropriate for the study type and the outcomes evaluated.
Domain 6: Outcome Measures and Results Display			

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Study Citation:	WIL Research, (2003). An inhalation reproduction/developmental toxicity screening study of 1,3-butadiene in rats.
Health Outcome(s) and Reported Health Effect(s):	Mortality-Mortality-Immune/Hematological-Macroscopic examination of the lymph nodes-Thyroid-Macroscopic examination of the thyroid glands-Gastrointestinal-Macroscopic examination of the abdominal and pelvic cavities-Other (please specify below) (Endocrine organs)-Pituitary weight
Duration and Exposure Route:	Inhalation-Vapor-Duration: Reproductive/Developmental-2-F0- premating (14 Days)-F0- mating (During 14-day mating period)-F0 - gestation (Throughout gestation until GD 20)-F0- lactation (From LD 5 until the day prior to euthanasia for a total of 60 to 70 days of exposure)-F1- post-natal (PND 21-27 or 28-34)-F0- premating (14 Days)-F0- mating (From LD 5 until the day prior to euthanasia for a total of 60 to 70 days of exposure)-F1- post-natal (PND 21-27 or 28-34)
Species:	Rat-Sprague-Dawley - [rat]-Both
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	10367501

Domain	Metric	Rating	Comments
Metric 8:	Endpoint sensitivity and specificity	High	The procedures were sensitive and specific for the outcomes measured and endpoints of interest.
Metric 9:	Results presentation	High	Results presentation appears to be appropriate for the study type and endpoints evaluated for data that are reported. Mean values for each group are provided with variance and incidence data are reported by group. Individual data are reported in appended sections.

Overall Quality Determination **High**