

GT3_MNT_MOUSE

	Element	Explanation
1.	QSAR identifier	
1.1.	QSAR identifier (title)	GT3_MNT_MOUSE, Micronucleus test, in vivo, Mouse, version 1.9.2.4.1286.350
1.2.	Other related models	This model is part of the set of CASE Ultra Genotoxicity models: GT2_CHROM_CHL(Chromosomal aberration in CHL cell line), GT2_CHROM_CHO(Chromosomal aberration in CHO cell line), GT4_ML_ACT (Mouse Lymphoma activated), GT4_ML_UNACT (Mouse Lymphoma unactivated)
1.3.	Software coding the model	<p>Name CASE Ultra Version 1.9.2.4</p> <p>URL http://www.multicase.com/case-ultra</p> <p>Description QSAR based bioactivity and toxicity prediction software.</p> <p>Contact sales@multicase.com, MultiCASE Inc, 5885 Landerbrook Dr. #210 Mayfield Heights, OH 44124 USA www.multicase.com</p>
2.	General information	
2.0.	Abstract	GT3_MNT_MOUSE is a statistical model for predicting micronucleus in vivo.
2.1.	Date of QMRF	July 2nd, 2019
2.2.	QMRF author(s) and contact details	<p>Name Mounika Girireddy</p> <p>Affiliation MultiCASE Inc.,</p> <p>Contact +1-440-565-7221</p> <p>URL www.multicase.com</p> <p>Email girireddy@multicase.com</p>
2.3.	Date of QMRF update(s)	March 27, 2024 October 15, 2025
2.4.	QMRF update(s)	<p>March 27, 2024 (all genotoxicity models were rebuilt and revalidated, Added data from FDA drug labels and echemportal (ECHA))</p> <p>October 15, 2025 (GT3_MNT_MOUSE model was rebuilt with two compounds from EFSA (European Food Safety Authority), Arena M, et al., 2018. Conclusion on the peer review of the pesticide risk assessment of the active substance BAS 750 F (mefentrifluconazole). EFSA Journal 2018;16(7):5379, 25 pp. https://doi.org/10.2903/j.efsa.2018.5379)</p>

2.5.	Model developer(s) and contact details	<p>Name Models were constructed under a Research Collaboration Agreement between the US Food and Drug Administration's Center for Drug Evaluation and Research, and MultiCASE Inc.</p> <p>Affiliation MultiCASE Inc.,</p> <p>Contact +1-440-565-7221</p> <p>URL www.multicase.com</p> <p>Email sales@multicase.com</p>
2.6.	Date of model development and/or publication	The original MC4PC model was developed in 2005; Published in 2005; Last update in 2014. In 2024 all the models were rebuilt and revalidated.
2.7.	Reference(s) to main scientific papers and/or software package	<ol style="list-style-type: none"> 1. Edwin J. Matthews, Naomi L. Kruhlak, Michael C. Cimino, R. Daniel Benz, Joseph F. Contrera. An analysis of genetic toxicity, reproductive and developmental toxicity, and carcinogenicity data: I. Identification of carcinogens using surrogate endpoints. <i>Regulatory Toxicology and Pharmacology</i> 44 (2006) 83–96. 2. Edwin J. Matthews, Naomi L. Kruhlak, Michael C. Cimino, R. Daniel Benz, Joseph F. Contrera. An analysis of genetic toxicity, reproductive and developmental toxicity, and carcinogenicity data: II. Identification of genotoxicants, reprotoxicants, and carcinogens using in silico methods. <i>Regulatory Toxicology and Pharmacology</i> 44 (2006) 97–110 3. Yoo JW, Minnier BL, Kruhlak NL, Stavitskaya L. Development of improved (Q)SAR models for predicting the outcome of the in vivo micronucleus genetic toxicity assay. Abstracts of Papers, 54th Society of Toxicology Annual meetings, San Diego CA, March 22-26, 2015, poster presentation. 4. Hewes KP, Stavitskaya L, Minnier BL, Kruhlak NL. Construction and application of (Q)SAR models to predict in vitro chromosome aberrations. Abstracts of Papers, 54th Society of Toxicology Annual meetings, San Diego CA, March 22-26, 2015, poster presentation. 5. FDA Drug Labels data from: Data provided by the U.S. Food and Drug Administration. https://open.fda.gov. 6. European Chemicals Agency. http://echa.europa.eu/ 7. EFSA (European Food Safety Authority): https://www.efsa.europa.eu/en
2.8.	Availability of information about the model	<p>Model is commercial. Although the training set is not publicly available, information about the non-proprietary training set chemicals, assay conditions and details, information about the alerts are available through CASE Ultra interface.</p> <p>For any other specific details contact: sales@multicase.com, MultiCASE Inc. 5885 Landerbrook Dr. #210 Mayfield Heights, OH 44124 USA. Phone: +1-440-565-7221.</p>

2.9.	Availability of another QMRF for exactly the same model	None
3	Defining the endpoint - OECD Principle 1: "A DEFINED ENDPOINT"	PRINCIPLE 1: "A DEFINED ENDPOINT". ENDPOINT refers to any physicochemical, biological, or environmental property/activity/effect that can be measured and therefore modelled. The intent of PRINCIPLE 1 (a (Q)SAR should be associated with a defined endpoint) is to ensure clarity in the endpoint being predicted by a given model, since a given endpoint could be determined by different experimental protocols and under different experimental conditions. It is therefore important to identify the experimental system and test conditions that is being modelled by the (Q)SAR.
3.1.	Species	In vivo micronucleus, mouse
3.2.	Endpoint	Group Genotoxicity Name Micronucleus in vivo Protocol As described in OECD 474.
3.3	Comment on endpoint	The mammalian in vivo micronucleus test is used for the detection of damage induced by the test substance to the chromosomes or the mitotic apparatus of erythroblasts, by analysis of erythrocytes as sampled in bone marrow and/or peripheral blood cells of animals, usually rodents (mice or rats). The purpose of the micronucleus test is to identify substances (liquid or solid) that cause cytogenetic damage which results in the formation of micronuclei containing lagging chromosome fragments or whole chromosomes. An increase in the frequency of micronucleated polychromatic erythrocytes in treated animals is an indication of induced chromosome damage. Animals are exposed to the test substance by an appropriate route (usually by gavage using a stomach tube or a suitable intubation cannula, or by intraperitoneal injection). Bone marrow and/or blood cells are collected, prepared and stained. Preparations are analyzed for the presence of micronuclei. Each treated and control group must include at least 5 analyzable animals per sex. Administration of the treatments consists of a single dose of test substance or two daily doses (or more). The limit dose is 2000 mg/kg/body weight/day for treatment up to 14 days, and 1000 mg/kg/body weight/day for treatment longer than 14 days.
3.4.	Endpoint units	Binary score
3.5.	Dependent variable	Overall Positive (1) or Negative (0). The final calls were determined as a summary of all the strains used in the test.
3.6.	Experimental protocol	As described in OECD 474.
3.7.	Endpoint data quality and variability	High quality curated data. Structures of training chemicals and names were verified. Duplicates were removed. Mixtures components were manually reviewed and used as separate entries if applicable.

4	Defining the algorithm - OECD Principle 2 : “AN UNAMBIGUOUS ALGORITHM”	PRINCIPLE 2: “AN UNAMBIGUOUS ALGORITHM”. The (Q)SAR estimate of an endpoint is the result of applying an ALGORITHM to a set of structural parameters which describe the chemical structure. The intent of PRINCIPLE 2 (a (Q)SAR should be associated with an unambiguous algorithm) is to ensure transparency in the model algorithm that generates predictions of an endpoint from information on chemical structure and/or physicochemical properties. In this context, algorithm refers to any mathematical equation, decision rule or output approach.
4.1.	Type of model	Model built using Statistical Machine Learning techniques. QSAR model with binary classification ability. Consists of a logistic regression model with molecular fragment/substructures as the descriptors. The descriptors cover both potentiating and deactivating/mitigating molecular features for compounds exhibiting or not-exhibiting genotoxic potential. The molecular features related to chromosome damage were identified from training data using various machine learning techniques.
4.2.	Explicit algorithm	<p>Definition Logistic regression QSAR</p> <p>Description Training: Multiple Logistic Regression model with occurrence of Alerts and Deactivating Features as independent and overall test outcome as dependent variable. Prediction: Application of the logistic regression model using the identification of alerts and modulators in the query compounds</p> <p>Ontology_term Training: Multi-parameter logistic regression modelling with occurrence of sub-structural features as independent and binary genotoxic potential as dependent variables. Prediction: Application of the logistic regression model using the identification of structural features in the query compounds and computing genotoxic potential using the fitted parameters of the model.</p>
4.3.	Descriptors in the model	<p>Name Molecular fragment-based descriptors.</p> <p>Units Count</p> <p>Description Occurrence of molecular fragment-based Alerts and modulating features as independent and overall test outcome as dependent variable.</p>
4.4.	Descriptor selection	A descriptor selection process was applied on the initial pool of molecular fragments which picks up the fragments with positive and negative contributions so as to give the best predictive ability to the whole model. The final model contains 186 alerts.
4.5.	Algorithm and descriptor generation	Descriptors for this CASE Ultra model are molecular fragments which are generated from splitting the training set compounds systematically and creating a dictionary of unique fragments. After selecting a few most relevant fragments, a statistical logistic regression data-fitting was applied

		between the X and Y variables to give the final model.
4.6.	Software name and version for descriptor generation	Name CASE Ultra Version 1.9.2.4 URL http://www.multicase.com/case-ultra Description QSAR based bioactivity and toxicity prediction software Contact sales@multicase.com, MultiCASE Inc, 5885 Landerbrook Dr. #210 Mayfield Heights, OH 44124 USA www.multicase.com
4.7.	Chemicals/Descriptors ratio	Number of Chemicals = 1286 (384 positives/902 negatives) Number of Descriptors = 186
5	Defining the applicability domain - OECD Principle 3: "A DEFINED DOMAIN OF APPLICABILITY"	PRINCIPLE 3: "A DEFINED DOMAIN OF APPLICABILITY". APPLICABILITY DOMAIN refers to the response and chemical structure space in which the model makes predictions with a given reliability. Ideally the applicability domain should express the structural, physicochemical and response space of the model. The CHEMICAL STRUCTURE (x variable) space can be expressed by information on physicochemical properties and/or structural fragments. The RESPONSE (y variable) can be any physicochemical, biological or environmental effect that is being predicted. According to PRINCIPLE 3 a (Q)SAR should be associated with a defined domain of applicability. Section 5 can be repeated (e.g., 5.a, 5.b, 5.c, etc) as many times as necessary if more than one method has been used to assess the applicability domain.
5.1.	Description of the applicability domain of the model	The applicability domain of the model is defined by fragment based chemical space defined by the training set chemicals and range in the computed prediction probabilities where the model has weakest differentiability.
5.2.	Method used to assess the applicability domain	The CASE Ultra program evaluates automatically whether a tested molecule is within the domain of applicability of the model it is tested with. A combination of two criteria were used: 1. Checking for 3-atom fragments that are not present in the training chemicals, and 2. Calculated prediction probabilities that fall between 0.27 - 0.36 where the model has weakest differentiability
5.3.	Software name and version for applicability domain assessment	Name CASE Ultra Version 1.9.2.4 URL http://www.multicase.com/case-ultra Description QSAR expert system for in-silico prediction of toxicity and bioactivity of chemicals. Contact sales@multicase.com, MultiCASE Inc, 5885 Landerbrook Dr. #210 Mayfield Heights, OH 44124 USA www.multicase.com
5.4.	Limits of applicability	Inorganic compounds, mixtures and large biomolecules are not covered. In addition, 1. Test chemicals with 3-atom fragments that are not present in the training chemicals potentially are out-of-domain, and

		2. Test chemicals with computed prediction probabilities between 0.30 - 0.36 are in grey zone
6	Defining goodness-of-fit and robustness (internal validation) – OECD Principle 4: “APPROPRIATE MEASURES OF GOODNESS-OF-FIT, ROBUSTNESS AND PREDICTIVITY”	PRINCIPLE 4: “APPROPRIATE MEASURES OF GOODNESS-OF-FIT, ROBUSTNESS AND PREDICTIVITY”. PRINCIPLE 4 expresses the need to perform validation to establish the performance of the model. GOODNESS-OF-FIT and ROBUSTNESS refer to the internal model performance.
6.1.	Availability of the training set	Training set data and associated references can be seen in CASE Ultra interface under “Display Training Set Chemicals”.
6.2.	Available information for the training set	a) Chemical names (common names and/or IUPAC names) b) CAS c) SMILES d) Mol
6.3.	Data for each descriptor variable for the training set	Some data available.
6.4.	Data for the dependent variable for the training set	Some data available.
6.5.	Other information about the training set	<p>Since the ratio of positives to negatives was not balanced, we considered adding some of the negatives as “extra coverage” compounds. This dataset contains: 384 positives, 902 negatives and 1036 extra coverage negatives. The compounds added as extra coverage negatives are predicted as “Known Negatives” but may not be found in the training set chemicals list. These chemicals can be found in the “ExtraNegCovgChems.dat” file under the model folder.</p> <p>Within CASE Ultra interface, all the alerts are supported by the training chemicals that are not proprietary. Every alert is supported by statistical details. e.g. number of positive and negative training chemicals that contain the fragment. Training set chemicals are explained with assay type, assay conditions, scientific publications etc.</p>
6.6.	Pre-processing of data before modelling	<ol style="list-style-type: none"> 1. Verification of chemical structures, registry numbers, CID and names. 2. Duplicates were removed. 3. Mixture components were treated on case-by-case basis, components if necessary were separated and assigned activity if possible.
6.7.	Statistics for goodness-of-fit	Sensitivity 93.0% Specificity 91.6% Positive predictivity 81.5% Negative predictivity 97.0%, Coverage 61.0% AUC 0.962, Self-validation, Classification cut-off 0.35
6.8.	Robustness - Statistics obtained by leave-one-out cross-validation	Not performed.

6.9.	Robustness - Statistics obtained by leave-many-out cross-validation	Sensitivity 88.4% Specificity 83.4% Positive predictivity 69.2% Negative predictivity 94.6%, Coverage 52.0% AUC 0.911, 10 iterations, 10% off Classification cut-off 0.35
6.10.	Robustness - Statistics obtained by Y-scrambling	Sensitivity 23.5% Specificity 66.7% Positive predictivity 21.1% Negative predictivity 69.3%, Coverage 31.7% AUC 0.430, 10 iterations, 10% off Classification cut-off 0.35
6.11.	Robustness - Statistics obtained by bootstrap	Sensitivity 89.3% Specificity 80.7% Positive predictivity 66.9% Negative predictivity 94.9%, Coverage 51.8% AUC 0.897, 10 iterations, 10% off Classification cut-off 0.35
6.12.	Robustness - Statistics obtained by other methods	Not performed
7	Defining predictivity (external validation) – OECD Principle 4: “APPROPRIATE MEASURES OF GOODNESS-OF-FIT, ROBUSTENESS AND PREDICTIVITY”	PRINCIPLE 4: “APPROPRIATE MEASURES OF GOODNESS-OF-FIT, ROBUSTENESS AND PREDICTIVITY”. PRINCIPLE 4 expresses the need to perform validation to establish the performance of the model. PREDICTIVITY refers to the external model validation. Section 7 can be repeated (e.g., 7.a, 7.b, 7.c, etc) as many times as necessary if more validation studies need to be reported in the QMRF.
7.1.	Availability of the external validation set	Not available.
7.2.	Available information for the external validation set	a) Chemical names (common names and/or IUPAC names) b) CAS c) SMILES
7.3.	Data for each descriptor variable for the external validation set	Some data available.
7.4.	Data for the dependent variable for the external validation set	Some data available.
7.5.	Other information about the external validation set	Not available.
7.6.	Experimental design of test set	The external set was composed of 75 compounds, 30 positive and 45 negatives. The external compounds were randomly selected from complete dataset (before splitting into training and test sets). Experimental protocol of the external compounds are same as the training set compounds.

7.7.	Predictivity - Statistics obtained by external validation	Sensitivity 44.44% Specificity 63.16% Positive predictivity 46.15% Negative predictivity 61.54%, Coverage 86.67% Concordance 55.38% Classification cut-off 0.35
7.8.	Predictivity - Assessment of the external validation set	Not available.
7.9.	Comments on the external validation of the model	Not available.
8	Providing a mechanistic interpretation - OECD Principle 5: "A MECHANISTIC INTERPRETATION, IF POSSIBLE"	PRINCIPLE 5: "A MECHANISTIC INTERPRETATION, IF POSSIBLE". According to PRINCIPLE 5, a (Q)SAR should be associated with a mechanistic interpretation, if possible.
8.1.	Mechanistic basis of the model	CASE Ultra models do not have any predefined knowledge of molecular mechanism that explains the activity of a molecule. However, the way the modules were built, splitting the entire learning set into clusters of molecules with a dedicated QSAR in every cluster, suggests very close links with a mechanistic explanations of activity. Indeed many of the resulting biophores have modes of action that are obvious to person with expert knowledge for the endpoint in question. For example, the presence of an alert containing N-nitroso fragment in bacterial mutagenicity model will undoubtedly suggest potential mutagenicity activity. Other fragments, which do not have such a clear mechanism of action assigned to them, can support an intelligent guess about possible sets of events causing activity. Either way, it is certain that the results of a MultiCASE analysis can serve as a mechanistic research tool as well as a QSAR builder.
8.2.	A priori or a posteriori mechanistic interpretation	The mechanistic basis of the model was neither determined a priori nor a posteriori. The selected features were mined completely automatically from the training data during the model building process and they agree very well with the known chemical mechanisms of genotoxicity. The training structures were also not selected with any specific mechanism in mind.
8.3.	Other information about the mechanistic interpretation	None.
9	Miscellaneous information	
9.1.	Comments	This model should be useful in the risk assessment of identifying compounds causing genotoxicity. It will also be helpful in understanding various known and unknown mechanisms of compounds causing genotoxicity. It will be particularly helpful in regulatory submission. When a prediction is made using this model in CASE Ultra program, the identified alerts (if any) are highlighted in the query chemical which is helpful in interpreting the results.
9.2.	Bibliography	1. Optimizing predictive performance of CASE Ultra expert system models using the applicability domains of individual toxicity alerts; Chakravarti, S.K., Saiakhov, R.D. and Klopman, G., Journal of Chemical Information and Modeling, 2012, 52, 2609-

		<p>2618. DOI: 10.1021/ci300111r.</p> <p>2. Effectiveness of CASE Ultra Expert System in Evaluating Adverse Effects of Drugs; Saiakhov, R.D., Chakravarti, S.K. and Klopman, G.; Molecular Informatics, 2012, 32, 87-97. DOI : 10.1002/minf.201200081.</p> <p>3. Computing similarity between structural environments of mutagenicity alerts, Chakravarti, S.K., Saiakhov, R. D.; Mutagenesis, October 20, 2018, DOI: https://doi.org/10.1093/mutage/gey032.</p>
9.3	Supporting information	Not available.