



**How does the GHS define germ cell mutagenicity?**

The GHS defines a germ cell mutagen as a chemical that may cause mutations in the germ cells of humans that can be transmitted to the progeny. A mutation is defined as a permanent change in the amount or structure of the genetic material in a cell. The terms mutagenic or mutagen are used to refer to those chemicals that cause an increased occurrence of mutations in populations of cells and/or organisms. Genotoxic is a more general term that applies to agents or processes which alter the structure, information content, or segregation of DNA, including those which cause DNA damage by interfering with normal replication processes, or which in a non-physiological manner temporarily alter its replication.

**How are germ cell mutagens classified under GHS?**

Under GHS, germ cell mutagens are classified in one of two categories based on the weight of evidence. Category 1 germ cell mutagens are those chemicals that are either known to induce or that should be regarded as if they induce heritable mutations. Category 2 germ cell mutagens are those that may induce heritable mutations.

Category 1 is subdivided based on whether the evidence is human epidemiological studies or other types of mutagenicity data (e.g. *in vivo* mammalian mutagenicity tests). See Table 1 below for hazard categories and hazard communication elements for germ cell mutagens.

**Table 1: Germ cell mutagen classification and hazard communication elements**

<b>Hazard Category</b>	<b>Category 1A</b>	<b>Category 1B</b>	<b>Category 2</b>
Category Description	Chemicals known to induce or regarded as if they induce heritable mutations in human germ cells	Chemicals known to induce or regarded as if they induce heritable mutations in human germ cells	Chemicals that may induce heritable mutations in human germ cells
Classification Criteria	Known to induce heritable mutations – positive evidence from human epidemiological studies	Regard as if they induce heritable mutations – positive results from <i>in vivo</i> heritable germ cell or somatic cell mammalian mutagenicity tests, or positive results showing mutagenic effects in the germ cells of humans without demonstration of transmission to progeny	Positive evidence obtained from <i>in vivo</i> somatic cell mutagenicity or somatic cell genotoxicity tests in mammals and in some cases with support from <i>in vitro</i> experiments
Symbol	 Health Hazard	 Health Hazard	 Health Hazard
Signal word	Danger	Danger	Warning
Hazard statement	May cause genetic defects (state route of exposure if it is)	May cause genetic defects (state route of exposure if it is conclusively proven that)	Suspected of causing genetic defects (state route of exposure if it is)

	conclusively proven that no other routes of exposure cause the hazard)	no other routes of exposure cause the hazard)	conclusively proven that no other routes of exposure cause the hazard)
Note: Table 1 provides basic criteria and is not a detailed summary. For the detailed official germ cell mutagen criteria consult the GHS.			

### Some Important Considerations in Classifying a Substance as a Mutagen

Classification should be based on the intrinsic ability of the chemical to induce mutations in germ cells based on the results of well conducted, sufficiently validated tests. All available evidence should be reviewed and evaluated using expert judgment. Classification should be made based on the total weight of evidence. See Table 2 for examples of tests that may be considered when evaluating germ cell mutagenicity data.

Table 2: Examples of mutagenicity / genotoxicity tests

Type of Test	Examples
<i>In vivo</i> heritable germ cell mutagenicity tests	Rodent dominant lethal mutation test (OECD 478) Mouse heritable translocation assay (OECD 485) Mouse specific locus test
<i>In vivo</i> somatic cell mutagenicity tests	Mammalian bone marrow chromosome aberration test (OECD 475) Mouse spot test (OECD 484) Mammalian erythrocyte micronucleus test (OECD 474)
Mutagenicity tests in germ cells	Mammalian spermatogonial chromosome aberration test (OECD 483) Spermatid micronucleus assay
Genotoxicity tests in germ cells	Sister chromatid exchange analysis in spermatogonia Unscheduled DNA synthesis test (UDS) in testicular cells
Genotoxicity tests in somatic cells	Liver Unscheduled DNA Synthesis (UDS) <i>in vivo</i> (OECD 486) Mammalian bone marrow Sister Chromatid Exchange (SCE)
<i>In vitro</i> mutagenicity tests	<i>In vitro</i> mammalian chromosome aberration test (OECD 473) <i>In vitro</i> mammalian cell gene mutation test (OECD 476) Bacterial reverse mutation test (OECD 471)

### Mixture Classification

Classification of mixtures is based upon available test data on individual ingredients of the mixture. A mixture is classified as a mutagen when at least one ingredient has been classified as a Category 1 or Category 2 mutagen and is present at or above the appropriate cut-off values/concentration limits for those categories (see Table 3). The classification may be modified on a case-by-case basis based on available test data for the mixture itself. Data on a mixture itself may be used when such data is conclusive and accounts for factors including dose, duration of study, observations, and analysis (statistical analysis, test sensitivity) of the germ cell mutagenicity test system. Bridging principles set forth in the GHS which are appropriate for classifying mixtures include: dilution, batching, and substantially similar mixtures.

Table 3: Concentration Limits Triggering Classification of Mixtures as Mutagens

Ingredient Classified as:	Cut-off/concentration limits triggering classification of a mixture as:	
	Category 1 mutagen	Category 2 mutagen
Category 1 mutagen	≥ 0.1%	-
Category 2 mutagen	-	≥ 1.0%

Note: Cut-off values apply to solids and liquids (w/w units) as well as gases (v/v units). If available data indicates that a hazard exists at levels below generic cutoffs, the mixture should be classified accordingly.

**To learn more ...**

- The GHS, in its entirety (including classification criteria and label and MSDS requirements), can be downloaded at: [http://www.unece.org/trans/danger/publi/ghs/ghs\\_rev03/03files\\_e.html](http://www.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html)
- OSHA's Notice of Proposed Rulemaking on the GHS is available at: [http://www.osha.gov/pls/oshaweb/owadisp.show\\_document?p\\_table=FEDERAL\\_REGISTER&p\\_id=21110](http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=FEDERAL_REGISTER&p_id=21110)
- A training course on the GHS is offered by the Society for Chemical Hazard Communication (SCHC): <http://www.schc.org/training.php>
- For information sheets on additional GHS topics:  
OSHA site: <http://www.osha.gov/dcsp/alliances/schc/schc.html#documents> - go to 'Products and Resources'.  
or SCHC site: [http://www.schc.org/issues.php?start\\_from=5&ucat=&archive=&subaction=&id=&cat=9](http://www.schc.org/issues.php?start_from=5&ucat=&archive=&subaction=&id=&cat=9) - see 'GHS Information Sheets'.
- The OSHA Guide to the Globally Harmonized System of Classification and Labeling of Chemicals is available at: <http://www.osha.gov/dsg/hazcom/ghs.html>

*The information contained in this sheet is believed to accurately represent provisions of U.S. regulations, consensus standards, and current GHS requirements (Revision 3). However, SCHC cannot guarantee the accuracy or completeness of this information. Users are responsible for determining the suitability and appropriateness of these materials for any particular application.*

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