Table 1. GHS classification on germ cell mutagens (1,2)

Category	Classification	Criteria
Category 1A	Chemicals known to induce heritable mutations in germ cells of humans	Positive evidence from human epidemiological studies.
Category 1B	Chemicals which should be regarded as if they induce heritable mutations in the germ cells of humans	—Positive result(s) from *in vivo* heritable germ cell mutagenicity tests in mammals; or —Positive result(s) from *in vivo* somatic cell mutagenicity tests in mammals, in combination with some evidence that the substance has potential to cause mutations to germ cells. This supporting evidence may, for example, be derived from mutagenicity/genotoxic tests in germ cells *in vivo*, or by demonstrating the ability of the substance or its metabolite(s) to interact with the genetic material of germ cells; or —Positive results from tests showing mutagenic effects in the germ cells of humans, without demonstration of transmission to progeny; for example, an increase in the frequency of aneuploidy in sperm cells of exposed people. Examples of *in vivo* heritable germ cell mutagenicity tests are: — Rodent dominant lethal mutation test — Mouse heritable translocation assay — Mouse specific locus test Examples of *in vivo* somatic cell mutagenicity test are: — Mammalian bone marrow chromosome aberration test — Mouse spot test — Mammalian erythrocyte micronucleus test Examples of mutagenicity/genotoxicity tests in germ cells are: (a) Mutagenicity tests: — Mammalian spermatogonial chromosome aberration test — Spermatid micronucleus assay (b) Genotoxicity tests: — Sister chromatid exchange analysis in spermatogonia — Unscheduled DNA synthesis test (UDS) in testicular cells
Category 2	Chemicals which cause concern for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans	—Positive evidence obtained from experiments in mammals and/or in some cases from *in vitro* experiments, obtained from: —Somatic cell mutagenicity tests *in vivo*, in mammals; or —Other *in vivo* somatic cell genotoxicity tests which are supported by positive results from *in vitro* mutagenicity assays. Examples of genotoxicity tests in somatic cells are: — Liver UDS *in vivo* — Mammalian bone marrow sister chromatid exchanges Examples of *in vitro* mutagenicity tests are: — *In vitro* mammalian chromosome aberration test — *In vitro* mammalian cell gene mutation test — Bacterial reverse mutation tests Note: Chemicals which are positive in *in vitro* mammalian mutagenicity assays, and which also show chemical structure activity relationship to known germ cell mutagens, should be considered for classification as Category 2 mutagens.

established in analogy to the categories for carcinogenic chemicals. Category 4 carcinogenic substances are those with non-genotoxic mechanisms of action. By definition, germ cell mutagens are genotoxic. MAK categories and criteria for classification of germ cell mutagens are summarized in Table 3.

The MAK Commission describes germ cell mutagenicity as follows (9): 'Germ cell mutagens produce heritable gene mutations, and heritable structural and numerical chromosome aberrations in germ cells. The consequences of germ cell mutations in subsequent generations include genetically determined phenotypic alterations without signs of illness, reduction in fertility, embryonic or perinatal death, more or less severe congenital malformations, and genetic diseases with various degrees of health impairment. The term "germ cell mutagenicity" refers specifically to mutagenicity in male and female germ cells and is distinguished from mutagenicity in somatic cells, which can initiate cancer. Epidemiological studies, however, have been unable to

Table 2. EU criteria for classification of chemicals as mutagenic (6,7)

Category	Classification	Criteria
Category 1	Substances known to be mutagenic to human	Positive evidence from human mutation epidemiology studies will be needed. Examples of such substances are not known to date.
Category 2	Substances which should be regarded as if they are mutagenic to human	Positive results from assays showing (a) mutagenic effects, or (b) other cellular interactions relevant to mutagenicity, in germ cells of mammals *in vivo*, or (c) mutagenic effects in somatic cells of mammals *in vivo* in combination with clear evidence that the substance or a relevant metabolite reaches the germ cells. With respect to placement in category 2, at present the following methods are appropriate:2(a) *In vivo* germ cell mutagenicity assays: — specific locus mutation test, — heritable translocation test, — dominant lethal mutation test. These assay actually demonstrate the appearance of affected progeny or a defect in the developing embryo. 2(b) *In vivo* assays showing relevant interaction with germ cells (usually DNA): — assays for chromosomal abnormalities, as detected by cytogenetic analysis, including aneuploidy, caused by malsegregation of chromosomes, — test for sister chromatid exchanges (SCEs), — test for unscheduled DNA synthesis (UDS), — assay of (covalent) binding of mutagen to germ cell DNA, — assaying other kinds of DNA damage. These assays provide evidence of a more or less indirect nature. Positive results in these assays would normally be supported by positive results from *in vivo* somatic cell mutagenicity assays, in mammals or in man. 2(c) *In vivo* assays showing mutagenic effects in somatic cells of mammals, in combination with toxicokinetic methods, or other methodologies capable of demonstrating that the compound or a relevant metabolite reaches the germ cells. For 2(b) and 2(c), positive results from host-mediated assays or the demonstration of unequivocal effects in *in vitro* assays can be considered as supporting evidence.
Category 3	Substances which cause concern for human owing to possible mutagenic effects.	There is evidence from appropriate mutagenicity studies, but this is insufficient to place the substance in category 2. Assays showing (a) mutagenic effects or (b) other cellular interaction relevant to mutagenicity, in somatic cells in mammals *in vivo*. The latter would be supported by positive results from *in vitro* mutagenicity assays. For effects in somatic cells *in vivo* at present the following methods are appropriate: 3(a) *In vivo* somatic cell mutagenicity assays: — bone marrow micronucleus test or metaphase analysis, — metaphase analysis of peripheral lymphocytes, — mouse coat color spot test. 3(b) *In vivo* somatic cell DNA interaction assays: — test for SCEs in somatic cells, — test for UDS in somatic cells, — assay for the (covalent) binding of mutagen to somatic cell DNA, — assay for DNA damage, e.g, by alkaline elution, in somatic cells. Substances showing positive results only in one or more *in vitro* mutagenicity assays should normally not be classified. Their further investigation using *in vivo* assays, however, is strongly indicated. In exceptional cases, e.g., for a substance showing pronounced responses in several *in vitro* assays, for which no relevant *in vivo* data are available, and which shows resemblance to known mutagens/carcinogens, classification in category 3 could be considered.

provide any evidence as yet that exposure to chemicals or to radiation results in hereditary diseases in man. Although structural changes have been demonstrated in the chromosomes of the germ cells of men exposed to radiation, even this finding can only provide indirect evidence that such exposures could lead to hereditary disorders in the offspring. The proof that an increased frequency of hereditary diseases is related to a particular exposure would be associated with great methodological difficulties. In the human population there are a large number of hereditary diseases of unknown origin with frequencies that differ widely in different subpopulations. Since mutational events occur largely randomly in the genome, it is not to be expected that one particular substance would induce one characteristic genetic disease. Therefore, it is most unlikely that proof of a

Table 3. Categories for classification of germ cell mutagens by MAK commission (8,9)

Category	Classification	Criteria
Category 1	Substances shown to increase the mutant frequency in the progeny of exposed humans	In the section 'Epidemiological methods and their limitations' it is explained why epidemiological studies to date have not been able to prove that the exposure of a particular human population to a particular substance has resulted in an increase in the incidence of inherited mutations. This is true both for ionizing radiation and chemical mutagens. Even if epidemiological methods are improved further, it is unlikely that such proof will be available in the foreseeable future. Category 1 will therefore probably remain without any entries.
Category 2	Substances shown to increase the mutant frequency in the progeny of exposed mammals	Classified as category 2 are substances that increase the incidence of genetically modified live progeny in animal studies, for example in the specific locus test or in the test for heritable translocations. Likewise, substances that should be classified as category 2 are those that increase the incidence of embryos that die in utero, for example in the dominant lethal test.
Category 3A	Substances shown to induce genetic damage in germ cells of humans or animals, or which produce mutagenic effects in somatic cells of mammals *in vivo* and shown to reach the germ cells in an active form	The methods include tests for genotoxicity in germ cells of experimental animals, such as tests for induction of structural chromosomal changes in spermatogonia or spermatocytes, for sister chromatid exchange in spermatogonia, for micronuclei in round spermatids, for numerical chromosome changes in secondary spermatocytes or in spermatozoa, for DNA single strand breaks and for repair synthesis or for covalent binding to the DNA. Also relevant are the observations obtained from exposed human populations which provide evidence for structural or numerical chromosome changes in spermatozoa of exposed persons. The development of new methods, especially molecular genetic methods for the detection of gene mutations in germ cells is to be expected. Substances that yield positive results in tests with germ cells are classified as category 3A. Also taken into account are clearly positive results from *in vivo* tests for mutagenicity in somatic cells, for example chromosomal aberrations or micronuclei in bone marrow cells, somatic mutations in the mammalian spot test or transgenic animals, provided that it has been demonstrated that the active substance or an active metabolite reaches the germ cells after relevant exposure of the experimental animals. Such substances are also suspected of being mutagenic in germ cells. Therefore they are classified as category 3A.
Category 3B	Substances suspected of germ cell mutagens because of their genotoxic effects in mammalian somatic cells *in vivo*; in exceptional cases, substances without *in vivo* data but with clearly mutagenic *in vitro* and structurally related to known *in vivo* mutagens	If the available data are not sufficient for classification in category 3A but the substance is clearly genotoxic in somatic cells of exposed animals or humans, the substance is also suspected of being mutagenic in germ cells. Substances that have yielded positive results in one or several *in vitro* mutagenicity tests generally not classified as category 3B. An exception is made for substances for which there are no relevant *in vivo* data but which are clearly genotoxic *in vitro* and also structurally related to substances known to be genotoxic *in vivo*. Such substances raise concern and are classified as category 3B.
Category 4	Not applicable	Category 4 carcinogenic substances are those with non-genotoxic mode of action. By definition, germ cell mutagens are genotoxic. Therefore, a category 4 for germ cell mutagens cannot exist. Depending on future research results, a category 4 could be defined at a later time for genotoxic substances with targets other than DNA (*i.e.*, pure aneugens).
Category 5	Substances considered the potency is considered so low, their contribution to genetic risk for man is expected not to be significant	Substances classified as category 5 are not expected to contribute significantly to the genetic risk for humans provided the MAK value is observed. For classification in this category, information on the spectrum of effects and their dose-dependence, and toxicokinetic data for species comparison are required. Biochemical and biological end-points can be used to characterize the contribution to genetic risk. The contribution to genetic risk is considered not to be significant after exposure at the workplace if the internal exposure level of the substance or its biomarkers is in the range of the background levels in a not specifically exposed reference population: @ Under workplace conditions the levels of biochemical effect markers such as DNA and protein adducts are not significantly increased above the background levels. @ Physiological-toxicokinetic model calculations based on animal data do not reveal a significant genetic risk for humans.

causal relationship between exposure to a chemical and occurrence of heritable diseases will become available in the foreseeable future. In this situation, for the identification of germ cell mutagens the results of animal experiments must be given particular attention. The mutagenic effect of chemicals on the germ cells of exposed parent animals can be demonstrated by observing an increased mutant frequency among the progeny. In addition, the demonstration of genotoxic effects of a substance in germ cells or somatic cells provides evidence of a potential hazard for subsequent generations.'

United States of America (US): *US EPA*: A classification using the following three categories of germ cell mutagens was proposed by the US Environmental Protection Agency (EPA) in 1984 for the evaluation of chemicals with respect to their ability to induce mutations in mammalian germ cells (10,11). Category I is based on sufficient evidence obtained from at least one *in vivo* mammalian germ cell mutation test or from at least two *in vivo* somatic cell mutation tests (point mutation and/or chromosomal aberrations), plus sufficient *in vivo* evidence that the chemical interacts with mammalian germ cells. Category II is based on suggestive evidence provided from positive results of *in vivo* somatic cell mutation tests plus evidence for interaction of the chemical with mammalian germ cells, but the evidence is insufficient to place the chemical in Category I. Category III is based on limited evidence of *in vivo* mutagenic activity or interaction of the chemical with mammalian germ cell DNA or other chromatin constituents. In 1986, guidelines for a "weight-of-evidence" approach to human germ cell mutagenicity were established, leading to eight categories with a decreasing order of strength of evidence (10). In addition, a "non-mutagen" category and a category for substances with inadequate evidence were described. The eight categories of evidence are as follows: (i) positive data derived from human germ cell mutagenicity studies; (ii) valid positive results from studies on heritable mutational events (of any kind) in mammalian germ cells; (iii) valid positive results from mammalian germ cell chromosome aberration studies that do not involve transmission from one generation to the next; (iv) sufficient evidence for a chemical's interaction with mammalian germ cells, together with valid positive mutagenicity test results from two assay systems, at least one of which is mammalian (*in vivo* or *in vitro*). The positive results may be both for gene mutation and chromosomal aberrations in mammalian systems; (v) suggestive evidence for a chemical's interaction with mammalian germ cells, together with valid positive mutagenicity evidence from two assay systems as described above under #iv. Alternatively, positive mutagenicity evidence of less strength than defined under #iv, when combined with sufficient evidence for a chemical's interaction with mammalian germ cells; (vi) positive mutagenicity test results of less strength than defined under #iv, combined with suggestive evidence for a chemical's interaction with mammalian germ cells; (vii) although definitive proof of non-mutagenicity is not possible, a chemical could be operationally classified as a non-mutagen for human germ cells if it gives valid negative test results for all endpoints of concern; and (viii) inadequate evidence bearing on either mutagenicity or chemical interaction with mammalian germ cells.

This system is for the classification for transmissible germ cell genetic risk. The Guideline (10) describes 'Evidence that an agent induces heritable mutations in human beings could be derived from epidemiologic data indicating a strong association between chemical exposure and heritable effects. It is difficult to obtain such data because any specific mutation is a rare event, and only a small fraction of the estimated thousands of human genes and conditions are currently useful as markers in estimating mutation rates. Human genetic variability, small numbers of offspring per individual and long generation times further complicate such studies. In addition, only disorders caused by dominant mutations, some sex-linked recessive mutations, and certain chromosome aberrations can be detected in the first generation after their occurrence. Conditions caused by autosomal recessive disorders (which appear to occur more frequently than dominant disorders) or by polygenic traits may go unrecognized for many generations. Therefore, in the absence of human epidemiological data, it is appropriate to rely on data from experimental animal systems as long as the limitations of using surrogate and model systems are clearly stated. Despite species differences in metabolism, DNA repair, and other physiological processes affecting chemical mutagenesis, the virtual universality of DNA as the genetic material and of the genetic code provides a rationale for using various nonhuman test systems to predict the intrinsic mutagenicity of test chemicals. Additional support for the use of nonhuman systems is provided by the observation that chemicals causing genetic effects in one species or test system frequently cause similar effects in other species or systems. Evidence also exists that chemicals can induce genetic damage in somatic cells of exposed humans. Furthermore, a wide variety of different types of mutations have been observed in humans, including numerical chromosome aberrations, translocations, base-pair substitutions, and frameshift mutations. Although the cause of these mutations is uncertain, it is clear from these observations that human germ-cell DNA is subject to the same types of mutational events that are observed in other species and test systems.'

***Recent US EPA proposals*:** Dearfield *et al.* from

Table 4. Proposed mutagenicity classification categories by US EPA researchers (12)

Classification	Criteria in Somatic cells	Criteria in Germ cells
Human mutagen	Positive in human somatic cell mutagenicity studies as a result of human *in vivo* exposure. May be human carcinogens; unless the risk characterization suggest not as likely. This can include cytogenetic endpoints in tissues (such as lymphocytes) from exposed persons.	Positive in human *in vivo* germ cell mutagenicity studies. Human germ cell mutagens. This is based on positive *in vivo* findings from appropriate germ cell targets in exposed humans. It is recognized that a human germ cell mutagen is not currently identified.
Probable human mutagen	Clear evidence for genotoxic activity *in vivo* mammalian test(s), usually supported by *in vitro* test(s). Usually animal carcinogens and may be human carcinogens. Classification at this level usually means that some *in vivo* testing has been performed as follow-up to positive results from *in vitro* testing. Therefore, there is usually some supporting positive evidence from *in vitro* testing.	Sufficient evidence of interaction with mammalian germ cells with clear evidence for genotoxic activity. Includes valid positive results from studies on heritable mutational events in mammalian germ cells; or, valid positive results from mammalian germ cell chromosomal aberration studies that do not include an intergeneration test. Putative human germ cell mutagens if they reach target cells. Alternatively, it should produce positive results for DNA strand breaks (e.g. comet test), UDS, SCE and/or chromosome aberrations in germinal cells.
Possible human mutagen	Some evidence for genotoxic activity. May be carcinogenic through genotoxic mechanisms; possibly in humans. Confirmed positive results may be seen in the *in vitro* test systems without supporting evidence from the *in vivo* assays. Agents falling into this category are considered to have intrinsic mutagenic potential which is not detected *in vivo*.	Suggestive evidence of interaction with mammalian germ cells with some evidence for genotoxic activity. May be putative human germ cell mutagens if they reach target cells. For a test agent to be considered to present suggestive evidence of germ cell interaction, data are needed to demonstrate that: (i) the test agent shows some evidence of somatic cell mutagenicity and/or genotoxicity; (ii) the test agent reaches the gonads (e.g. data from pharmacokinetic/tissue distribution studies of the test agent and/or metabolites); (iii) the test agent interacts with germinal cells; these data come from subchronic or chronic toxicity tests showing gonadal pathology (e.g. sperm abnormalities); and (iv) the test agent causes adverse effects on reproductive parameters (e.g. decreased fertility, increased dead implants, reduced litter sizes).
Equivocal evidence	Results from acceptable tests that cannot be convincingly called negative or positive.	
Negative evidence	Negative results in acceptable tests.	

the US EPA proposed 6 categories of mutagenicity classification that are divided to 3 categories each for somatic cells and germ cells (12). This includes (i) human somatic cell mutagens in which positive data in human somatic cells are derived from studies with exposed humans that gives positive data in human; (ii) human germ cell mutagen in which positive data from human *in vivo* germ cell studies are obtained; (iii) probable human somatic cell mutagen in which clear evidence for genotoxic activity from positive *in vivo* mammalian test(s); (iv) probable human germ cell mutagen in which sufficient evidence of interaction with mammalian germ cells with clear evidence for genotoxic activity; (v) possible human somatic cell mutagen in which confirmed positive results may be seen in the *in vitro* test systems without supporting evidence from the *in vivo* assays; and (vi) possible human germ cell mutagen in which suggestive evidence of interaction with mammalian germ cells is seen. The mutagenicity classification categories proposed by Dearfield *et al.* (12) are summarized in Table 4.

The mutagenicity/genotoxicity data organized into "clear" and "some" evidence for mutagenicity and into "suggestive" and "sufficient" evidence germ cell interaction. The classification of mutagenicity results falls into the broad categories of inadequate, negative, equivocal, and positive data. With respect to the effects of mutagens, Dearfield *et al.* stated that 'In addition to cancer, adverse health effects from somatic cell mutations and/or germ cell mutations include sickle cell anemia, cardiovascular disease, reproductive/developmental effects, and neurobehavioral effects among many specific and general endpoints, as well as having impact on the aging process.' (12).

Canada: *Health Canada*: Health Canada proposed 6 categories of classification of chemicals with respect to

their mutagenic potential for germ cells in the Canadian Environmental Protection Act (CEPA), Human Health Risk Assessment for Priority Substances (13). Four categories have several subgroups based on the degree of evidence (Table 5). These classifications are as follows: human germ cell mutagen (group I), for which data from adequate epidemiological studies indicate that there is a causal relationship between exposure of humans to a chemical and an increased incidence of inherited mutations in live or dead offspring; probable human germ cell mutagen (group II), for which data from epidemiological studies to assess germ cell mutagenicity are inadequate: however, there is sufficient evidence of germ cell mutagenicity in animal species (*i.e.*, there is an increased incidence of gene mutations, structural or numerical chromosomal aberrations, or inherited congenital malformations in the live offspring of exposed animals; or an increase in dominant lethal mutations in the potential offspring of exposed animals); possible human germ cell mutagen (group III); unlikely to be a human germ cell mutagen (group IV); probably not a human germ cell mutagen (group V); unclassifiable with respect to germ cell mutagenicity in humans (group VI). Groups III, IV, V and VI have four, two, three and three subgroups, respectively (see Table 5).

The Canadian Environmental Protection Act (13) mentions 'These effects including mutagenic are manifested at the biochemical, cellular, histopathological and morphological levels.', and 'Chemical substances are classified, therefore, with respect to their potential carcinogenicity and mutagenicity to humans; this is accomplished on the basis of rigorous examination of the quantity, quality and nature of the results of available toxicological and epidemiological studies. The criteria by which Priority Substances are classified based on their weight of evidence of carcinogenicity and mutagenicity.'

Health Protection Branch: The Health Protection Branch defined toxicological findings that would be regarded as germ cell genotoxicity (14). The toxicological indication of germ cell genotoxicity are (i) *in vitro* test results and positive evidence for mutagenicity in somatic cells *in vivo*, and (ii) evidence from pharmacokinetic/tissue distribution studies that the test material and/or metabolites reaches the gonads; or (iii) evidence from subchronic or chronic treatment studies that gonadal pathology indicates germ cell damage; or (iv) evidence for reproductive/developmental effects showing reduced numbers of pregnancies, reduced litter sizes or increased time to mating following treatment in some cases. A significant proportion of agents that cause *in vivo* somatic cell mutation might also possess the ability to lead to mutation in germ cells that may be transmitted to offspring. When evidence for *in vivo* somatic genotoxicity is demonstrated, along with tissue distribution, metabolic and/or pathologic evidence that the genotoxic chemical (or metabolites) reaches the germ lines (whether or not overt effects on fertility are found), the possibility of induced genetic damage to germ cells leading to heritable effects should be investigated (14).

Canadian Centre for Occupational Health and Safety: Controlled Products Regulations (CPR) has two mutagenicity criteria (11,15). According to CPR paragraph 57 in the classification of subdivision A (very toxic material), a chemical or chemical mixture is considered to present a hazard to man if (a) there is epidemiological evidence that shows a causal connection between exposure of persons to the substance or mixture and heritable genetic effects; or (b) there is evidence of mutagenicity in mammalian germ cells *in vivo* as shown by (i) positive results in a study that measures mutations transmitted to offspring, or (ii) positive results in an *in vivo* study showing chemical interaction with the genetic material of mammalian germ cells and positive results in an *in vivo* study assessing either gene mutation or chromosomal aberration in somatic cells. CPR paragraph 62 in the classification of subdivision B (toxic material) explains that a pure chemical or a chemical mixture is considered to present a hazard if evidence of mutagenicity in mammalian somatic cells is obtained in a test to assess either gene mutations or chromosomal aberrations.

Japan: The Japanese Industrial Safety and Health Law addresses the mutagenicity classification of substances in the workplace (11). Under this legislation, Japan does not classify mutagenic substances according to a weight of evidence approach or whether a compound may be a somatic or germ cell mutagen but rather recognizes one category: "mutagenic". A substance is classified as mutagenic when the results of a "bacterial reverse mutation assay" are positive. Workers' health impairment by the exposure to the 'strong' mutagenic chemicals or chemical mixtures (excluding those containing 1% or less by weight of mutagenic chemicals), which induce more than 1000 revertants/mg/plate in a bacterial reverse mutation assay, should be prevented in the work for manufacture or handling of these chemicals (16).

Future of Classification of Germ Cell Mutagens

Chemical evaluation of mutagenicity/genotoxicity has three major directions that are (i) screening of carcinogens, (ii) mechanistic investigation of carcinogenesis, and (iii) investigation of heritable adverse effects in germ cells including those in humans. Mutagenicity in GHS is focused on the last topic in terms of classification of germ cell mutagens. GHS and the other existing classification systems have different

Table 5. Criteria for classification of mutagenicity in germ cells in CEPA by Health Canada (13)

Category	Classification	Criteria
Group I	Human Germ Cell Mutagen	Data from adequate epidemiological studies indicate that there is a causal relationship between exposure of humans to a substance and an increased incidence of inherited mutations in live or dead offspring.
Group II	Probable Human Germ Cell Mutagen	Data from epidemiological studies to assess germ cell mutagenicity are inadequate: however, there is sufficient evidence of germ cell mutagenicity in animal species (i.e., there is an increased incidence of gene mutations, structural or numerical chromosomal aberrations, or inherited congenital malformations in the live offspring of exposed animals; or an increase in dominant lethal mutations in the potential offspring of exposed animals).
Group III. A	Possible Human Germ Cell Mutagen	Data from epidemiological studies indicate an association between exposure and human germ cell mutagenicity, but alternative explanations such as chance, bias, or confounding cannot be excluded.
Group III. B	ditto	Data from epidemiological studies to assess germ cell mutagenicity are inadequate: however, there is sufficient evidence of somatic cell mutagenicity (*in vivo* gene mutations or chromosomal aberrations) in humans or animal species, and sufficient evidence of exposure to germ cells in humans or animal species.
Group III. C	ditto	Data from epidemiological studies to assess germ cell mutagenicity in humans are inadequate or lacking. There is sufficient data in animals to indicate that the chemical is a germ cell mutagen, but available data indicate that the induction of mutations occurs through an epigenetic threshold-based mechanism.
Group III. D	ditto	Data from epidemiological studies to assess germ cell mutagenicity in humans are inadequate. There is sufficient evidence of mutagenicity of somatic cells in humans or animal species (*in vivo* gene mutations or chromosomal aberrations), but evidence of exposure to germ cells is inadequate or lacking.
Group IV. A	Unlikely to Be a Human Germ Cell Mutagen	There is no evidence of human germ cell mutagenicity in sufficiently powerful and well-designed epidemiological studies. There is evidence of mutagenicity of somatic cells in well-designed and well-conducted studies in humans or animals, but there is no evidence of exposure of human or animal germ cells in well-designed studies.
Group IV. B	ditto	Data on germ cell mutagenicity in epidemiological studies in humans are inadequate; there is no evidence of mutagenicity *in vivo* in germ or somatic cells in well-designed and properly conducted studies in animals.
Group V. A	Probably Not a Human Germ Cell Mutagen	There is no evidence of germ cell mutagenicity in sufficiently powerful and well-designed epidemiological studies; there is no evidence of germ cell mutagenicity in animal species.
Group V. B	ditto	There is no evidence of germ cell mutagenicity in sufficiently powerful and well-designed epidemiological studies; data in animal species are inadequate.
Group V. C	ditto	Data from epidemiological studies to assess germ cell mutagenicity in humans are inadequate, but evidence of the lack of germ cell mutagenicity in animal species is strongly supported by other data on mutagenicity *in vivo*.
Group VI. A	Unclassifiable with Respect to Germ Cell Mutagenicity in Humans	Data from epidemiological and/or animal studies are inadequate (i.e., because of major qualitative limitations, the studies cannot be interpreted as showing either the presence or absence of germ cell mutagenicity).
Group VI. B	ditto	There are no *in vivo* mutagenicity data available for evaluation.
Group VI. C	ditto	Results of epidemiological studies in human populations and experimental studies in animal species are conflicting, without an identifiable mechanistic basis.

objectives, target audiences and criteria. For example, the primary objective of the systems in GHS, EU and Germany MAK is for hazard classification, on the other hand, the systems of US EPA and Health Canada are for risk assessment. Target audiences are workers in the systems of Germany MAK, Canadian CPR and Japan; consumers and workers in EU system; consumers, workers, transport workers, and emergency responders in GHS. As for criteria, the report from EPA researchers includes adverse effects on reproductive

parameters.

The fundamental purposes are different in these regulations; therefore, it is difficult to discuss the significance of the different approaches. Simple classification category and criteria will be useful for hazard classification. The GHS and EU systems on (germ cell) mutagenicity meet to this point. Application of the criteria needs expert judgment in a weight of evidence approach in GHS. However, the expert judgment leads sometimes different conclusion from expert to expert. This will be a critical issue in the classification of germ cell mutagens by GHS. Furthermore, hazard classification/evaluation is often confused as risk evaluation, especially in Japan. Further efforts including risk evaluation and communication on germ cell mutagenicity will be needed to make understanding of regulations global.

Recently, the European Commission proposed a new regulatory framework for chemicals called REACH for the Registration, Evaluation and Authorisation of Chemicals in October 2003 (17). The authorisation process pays particular attention to the risks that the substance poses due to any carcinogenic, mutagenic, and/or reproductive toxicity (CMR) properties. CMR's category 1 and 2 in the EU criteria, which correspond to the category 1A and 1B, respectively in GHS criteria, are subject to authorization (18,19). All substances imported in quantities over 1 tonne that contain more than 0.1 per cent CMR material must be authorised before gaining access to the EU market. Authorisation provides a permit for specific uses and can be requested by 'producer' or 'user'. The GHS itself is not legally binding, however, some national or regional laws including REACH may be legally binding. Now, classification of germ cell mutagens becomes an important issue.

As GHS criteria have been adopted in worldwide, it will become standard for hazard classification. After implementation of GHS in each country, the classification of chemicals on germ cell mutagenicity will be performed by chemical suppliers (manufacturers or importers). Understanding classification systems for germ cell mutagens will be helpful for scientifically sound classification of chemicals in the GHS.

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化学品の分類および表示に関する世界調和システム(GHS).
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