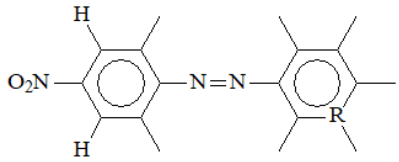
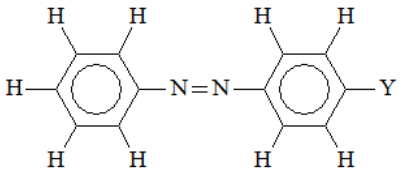
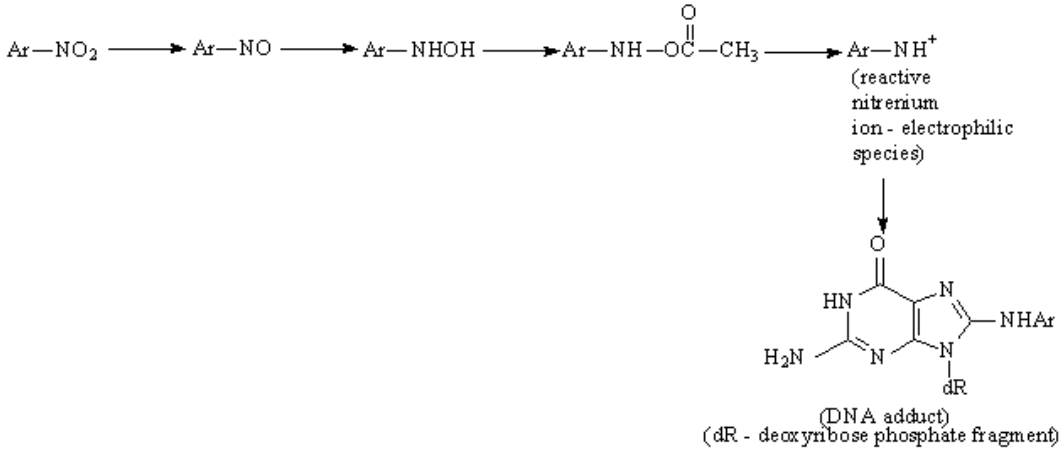
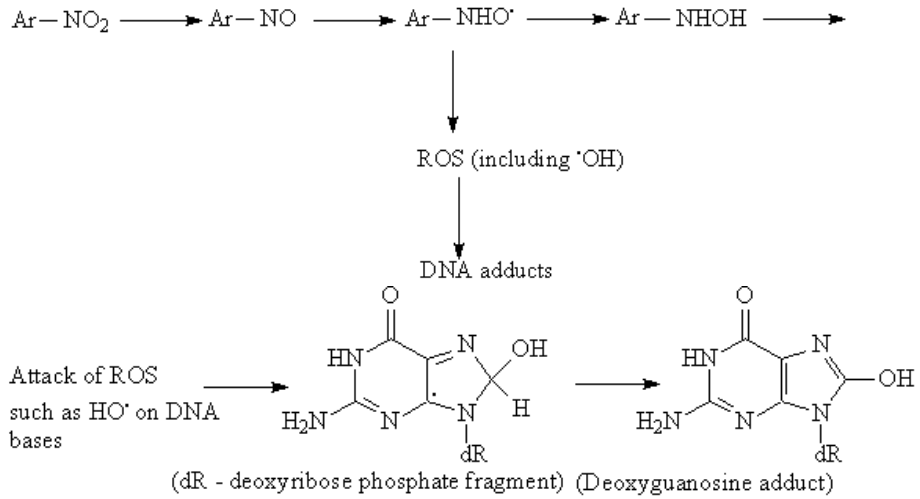
Individual profile/alert	
Name	Nitro Azoarenes and p-Monosubstituted Azobenzene Derivatives
Type of profile	Structural alert
Description/applicability domain	 R = any carbon or nitrogen, single arene ring only, no fused ring fragments in the molecular structure  Y= NH_2 or OH
Mechanism	**Heterolytic Mechanism.** This is the most important mechanism, associated with the bacterial mutagenicity of nitroarenes, and, particularly, the sub-class discussed here. The DNA damage, eliciting bacterial mutagenicity results mainly from covalent adduct formation. It arises from several activated metabolites, including the N-hydroxylamine (proximate mutagenic form) and its O-esterified derivative formed by phase II (O-acetylation, sulfation) enzymatic reaction with the subsequent generation of electrophilic nitrenium ion. The latter species may exert electrophilic attack on DNA bases. (**Nucleophilic attack after reduction and nitrenium ion formation)** **Radical (Homolytic) Mechanism.** This is one of the mechanisms (but not the most important) for eliciting bacterial mutagenicity of nitro compounds. Certain monocyclic and polycyclic aromatic nitro compounds (ArNO2) are implicated in carcinogenesis. Reduction of the nitro to the nitroso intemediate is followed by formation of N-hydroxylamine species and may occur in the prokaryotic Salmonella typhimurium cell. Several transient radical intermediates, including reactive oxygen species (ROS) are formed during this process, and have been found to cause oxidative DNA damage (strand breaks) **(Radical mechanism *via* ROS formation (indirect)**
Heterolytic	

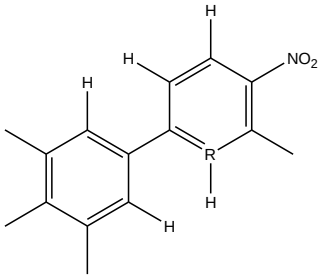
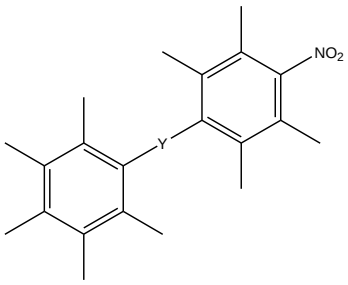


Radical (Homolytic) Mechanism



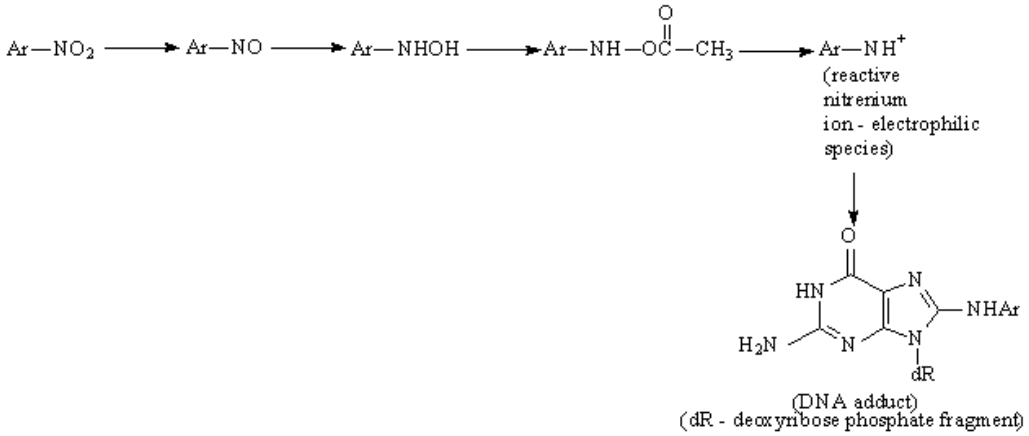
Set of chemicals used for profile development	Nitro Azoarenes and p-Monosubstituted Azobenzene Derivatives
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1.Sabbioni, Envir. Health Persp. **102**, Suppl. 6 (1994), 61 – 67. 2.Kalgutkar, Current Drug Metabol. **6** (2005), 161 – 225. 3.Aiub, Chem.-Biol. Interact. **161** (2006), 146 – 154. 4.Einisto, Mutat. Res. **259** (1991), 95 – 102. 5.Kovacic, Current Med. Chem. **8**, (2001), 773 – 796. 6.Witherell, Canc. Epidemiol. Biomarkers & Prevention **7** (1998), 91 – 96. 7.Wiseman, Biochem. J. **313** (1996), 17 – 29. 8.Purohit, Chem. Res. Toxicol. **13**(8) (2000), 673 – 692. 9.Zbaida, S., J. Pharmacol. Exp. Ther. **260**(2) (1992), 554 – 561 10.*4-Nitroazobenzene*, GENE-TOX; http://toxnet.nlm.nih.gov/cgi-bin/sis/search/r?dbs+genetox:@term+@rn+@rel+"2491-52-3". 11.Chung, Mutat. Res. **277** (1992), 201 – 220. 12.Gunkel, A. M., *Evaluation of the Mutagenicity and Toxicity of Monoazo Dyes in Wastewater Effluents and Sludge Supernatans*

	(Abstract); 13.Bakshi, J. Environ. Pathol. Toxicol. Oncol. 22(2) (2003), 101 – 109; http://www.ncbi.nlm.nih.gov/pubmed/14533873). 14. Morita, T., Mutat. Res. 802 (2016), 1 – 29. 15. Mori, H., Cancer Res. **46**, 1986, 1654 - 1658. 16. Hashimoto, Y., Gan. 72(6) (1981), 921 – 929 (Abstract); https://www.ncbi.nlm.nih.gov/pubmed/7042447 17. Lang, B., Mutat. Res. **191** (1987), 139 – 143. 18. Shamovsky, I., JACS **133** (2011), 16168 – 16185.

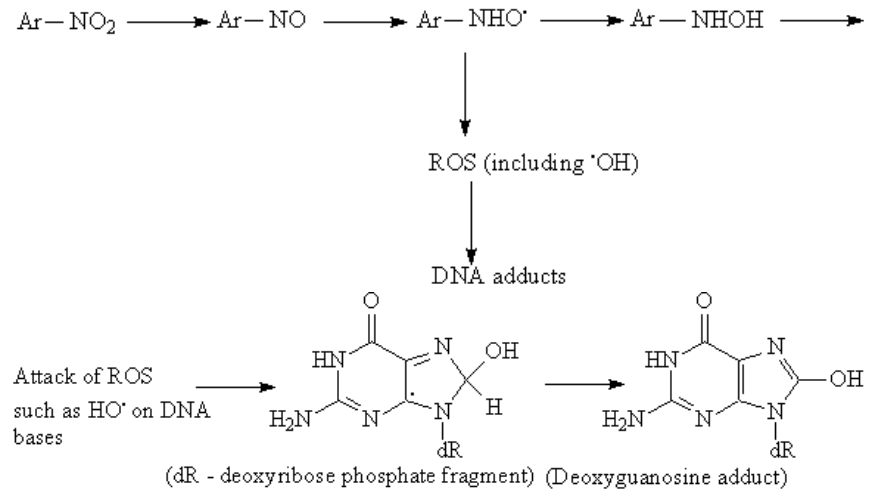
Individual profile/alert	
Name	Nitrobiphenyls and Bridged Nitrobiphenyls
Type of profile	Structural alert
Description/applicability domain	**Nitrobiphenyl**  **R= C or N(aromatic)** **o-distributed nitrobiphenyl are excluded** **Bridged Nitrobiphenyl**  **Y= O, S(V2), Ethyl, Ethene**
Mechanism	**Heterolytic Mechanism.** This is the most important mechanism, associated with the bacterial mutagenicity of nitroarenes, and, particularly, the sub-class discussed here. The DNA damage, eliciting bacterial mutagenicity results mainly from covalent adduct formation. It arises from several activated metabolites, including the N-hydroxylamine (proximate mutagenic form) and its O-esterified derivative formed by phase II (O-acetylation, sulfation) enzymatic reaction with the subsequent generation of electrophilic nitrenium ion. The latter species may exert electrophilic attack on DNA bases. (**Nucleophilic attack after reduction and nitrenium ion formation)** **Radical (Homolytic) Mechanism.** This is one of the mechanisms (but not the most important) for eliciting bacterial mutagenicity of

	nitro compounds. Certain monocyclic and polycyclic aromatic nitro compounds (ArNO2) are implicated in carcinogenesis. Reduction of the nitro to the nitroso intemediate is followed by formation of N-hydroxylamine species and may occur in the prokaryotic Salmonella typhimurium cell. Several transient radical intermediates, including reactive oxygen species (ROS) are formed during this process, and have been found to cause oxidative DNA damage (strand breaks) **(Radical mechanism *via* ROS formation (indirect)**

Heterolytic

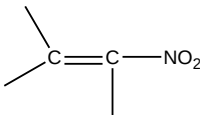
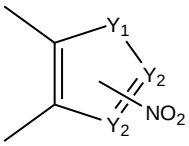


Homolytic



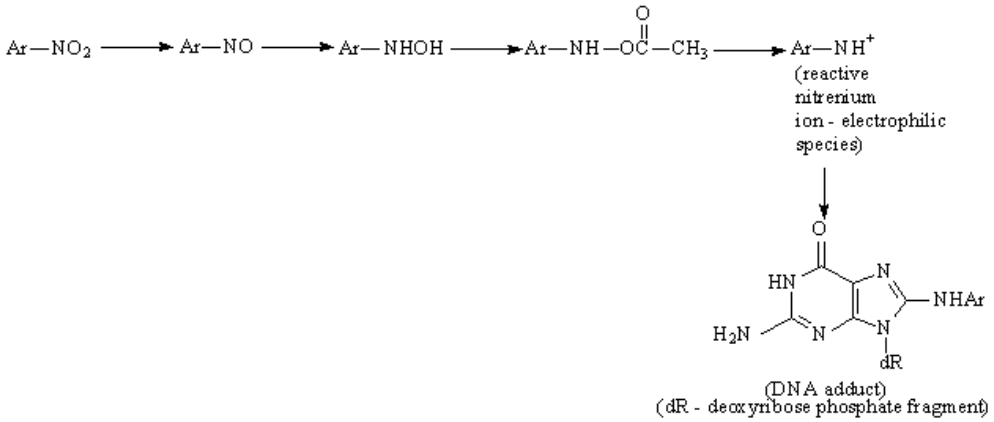
Set of chemicals used for profile development	Nitrobiphenyls and Bridged Nitrobiphenyls
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1.Sabbioni, Envir. Health Persp. **102**, Suppl. 6 (1994), 61 – 67. 2.Kalgutkar, Current Drug Metabol. **6** (2005), 161 – 225.

	3.Aiub, Chem.-Biol. Interact. **161** (2006), 146 – 154. 4.Einisto, Mutat. Res. **259** (1991), 95 – 102. 5.Kovacic, Current Med. Chem. **8**, (2001), 773 – 796. 6.Witherell, Canc. Epidemiol. Biomarkers & Prevention **7** (1998), 91 – 96. 7.Wiseman, Biochem. J. **313** (1996), 17 – 29. 8.Purohit, Chem. Res. Toxicol. **13**(8) (2000), 673 – 692. 9. El-Bayoumy, Mutat. Res. **81** (1981), 143 – 153. 10. Vance, Environ. Mutagen, **6** (6) (1984), 797 – 811). 11. *Chemical Carcinogenesis Research Information System (CCRIS)* http://toxnet.nlm.nih.gov/cgi-bin/sis/search/r?dbs+ccris:@term+@rn+620-88-2. 12. Juneja, Mutat. Res. **263 (**9) (1991), 13 – 19. 13. Hooberman, Mutat. Res. **341** (1994), 57 – 69.

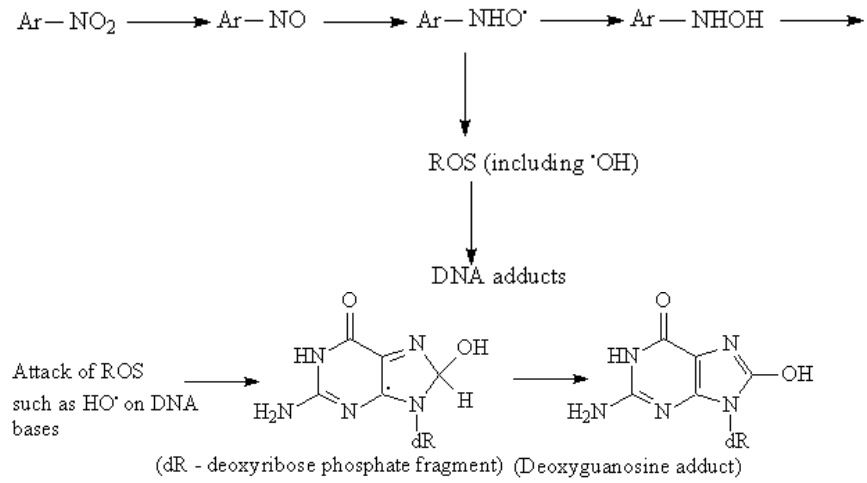
Individual profile/alert	
Name	Conjugated Nitroalkenes and Five Membered Aromatic Nitroheterocyclics
Type of profile	Structural alert
Description/applicability domain	**Characteristic active structural fragment**  **More specifically defined active structural fragment**  **R_1= N(V3)(sp^3) or S(V2) or O** **R_2= N(V3)(sp^2) or C(sp^2)**
Mechanism	**Heterolytic Mechanism.** This is the most important mechanism, associated with the bacterial mutagenicity of nitroarenes, and, particularly, the sub-class discussed here. The DNA damage, eliciting bacterial mutagenicity results mainly from covalent adduct formation. It arises from several activated metabolites, including the N-hydroxylamine (proximate mutagenic form) and its O-esterified derivative formed by phase II (O-acetylation, sulfation) enzymatic reaction with the subsequent generation of electrophilic nitrenium ion. The latter species may exert electrophilic attack on DNA bases.(**Nucleophilic attack after reduction and nitrenium ion formation)** **Radical (Homolytic) Mechanism.** This is one of the mechanisms (but not the most important) for eliciting bacterial mutagenicity of nitro compounds. Certain monocyclic and polycyclic aromatic nitro compounds (ArNO2) are implicated in carcinogenesis. Reduction of

	the nitro to the nitroso intemediate is followed by formation of N-hydroxylamine species and may occur in the prokaryotic Salmonella typhimurium cell. Several transient radical intermediates, including reactive oxygen species (ROS) are formed during this process, and have been found to cause oxidative DNA damage (strand breaks) **(Radical mechanism *via* ROS formation (indirect)**

Heterolytic

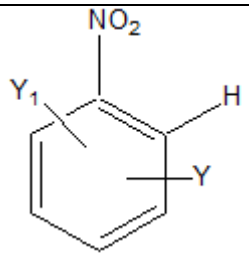


Homolytic



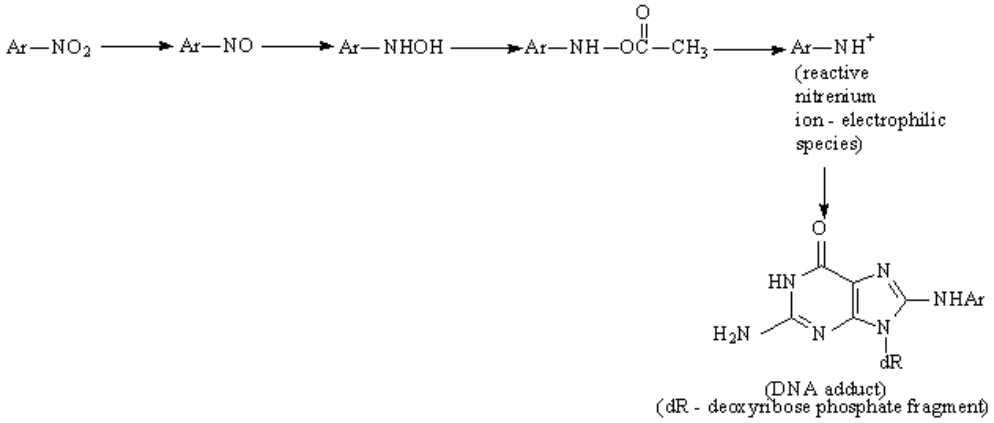
Set of chemicals used for profile development	Conjugated Nitroalkenes and Five-Membered Aromatic Nitroheterocyclics
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1.Sabbioni, Envir. Health Persp. **102**, Suppl. 6 (1994), 61 – 67. 2.Kalgutkar, Current Drug Metabol. **6** (2005), 161 – 225. 3.Aiub, Chem.-Biol. Interact. **161** (2006), 146 – 154. 4.Einisto, Mutat. Res. **259** (1991), 95 – 102. 5.Kovacic, Current Med. Chem. **8**, (2001), 773 – 796. 6.Witherell, Canc. Epidemiol. Biomarkers & Prevention **7** (1998), 91 –

	96. 7.Wiseman, Biochem. J. **313** (1996), 17 – 29. 8.Purohit, Chem. Res. Toxicol. **13**(8) (2000), 673 – 692. 9. Ebringer, Folia Microbiol. **25** (1996), 388 – 396. 10. *Metronidazole*, Chemical Carcinogenesis Research Information System; http://toxnet.nlm.nih.gov/cgi-bin/sis/search/r?dbs+ccris:@term+@rn+443-48-1.". 11. Wang, Canc. Res. **35** (1975), 3611 – 3617. 12. Ramos, Mutat. Res. **390** (1997), 233 – 238. 13. CCRIS: Benznidazole CASRN: 22994-85-0, Toxicology Data Network, U.S. National Library of Medicine**;** http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+ccris:@term+@rn+22994-85-0. 14. Gene-Tox: Misonidazole CASRN: 13551-87-6, Toxicology Data Network, U.S. National Library of Medicine; http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+genetox:@term+@rn+@rel+13551-87-6 15. Buschini, A., L. Ferrarini, S. Franzoni, S. Galati, M. Lazzaretti, Fr. Mussi, Cr. N. Albuquerque, T. M. A. D. Zucchi, P. Poli, Genotoxicity Revaluation of Three Commercial Nitroheterocyclic Drugs: Nifurtimox, Benznidazole, and Metronidazole, J. Parasitolog. Res. 2009; doi:10.1155/2009/463575. 16. McMahon, R. E., J. C. Cline, Chr. Z. Thompson, Assay of 855 Test Chemicals in Ten Tester Strains Using a New Modification of the Ames Test for Bacterial Mutagens, Canc. Res. 39 (1979), 682 – 693.

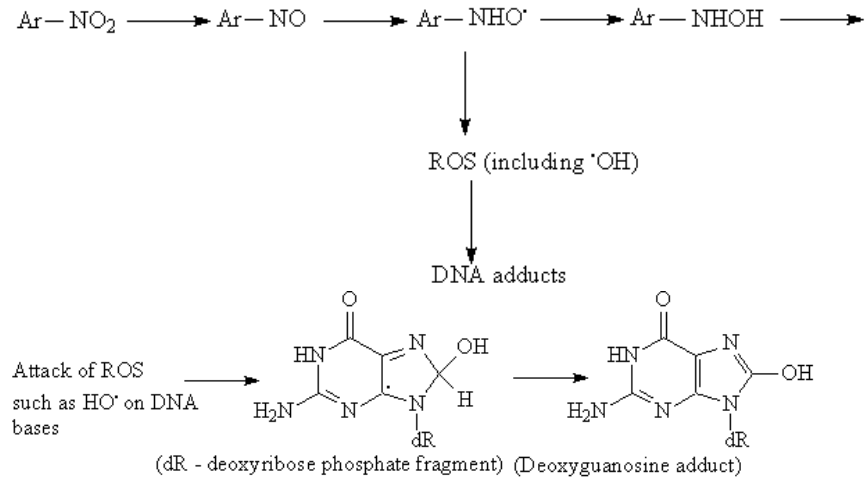
Individual profile/alert	
Name	Nitroaniline Derivatives
Type of profile	Structural alert
Description/applicability domain	 Y is $N_{(v3)}sp^3$ (Primary, secondary or tertiary amino group) Y_1= NO_2 or $N_{(v3)}Hsp^3$ or $OCsp^3$(3 or less per chain) or OH or C or CN or Cl or Br or H
Mechanism	**Heterolytic Mechanism.** This is the most important mechanism, associated with the bacterial mutagenicity of nitroarenes, and, particularly, the sub-class discussed here. The DNA damage, eliciting bacterial mutagenicity results mainly from covalent adduct formation. It arises from several activated metabolites, including the N-hydroxylamine (proximate mutagenic form) and its O-esterified derivative formed by phase II (O-acetylation, sulfation) enzymatic reaction with the subsequent generation of electrophilic nitrenium ion. The latter species may exert electrophilic attack on DNA bases.(**Nucleophilic attack after reduction and nitrenium ion formation)**

	Radical (Homolytic) Mechanism. This is one of the mechanisms (but not the most important) for eliciting bacterial mutagenicity of nitro compounds. Certain monocyclic and polycyclic aromatic nitro compounds (ArNO2) are implicated in carcinogenesis. Reduction of the nitro to the nitroso intemediate is followed by formation of N-hydroxylamine species and may occur in the prokaryotic Salmonella typhimurium cell. Several transient radical intermediates, including reactive oxygen species (ROS) are formed during this process, and have been found to cause oxidative DNA damage (strand breaks) **(Radical mechanism *via* ROS formation (indirect)**

Heterolytic

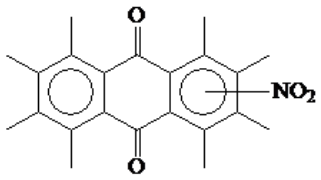
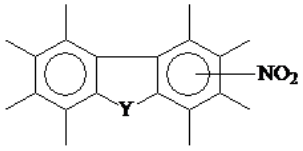
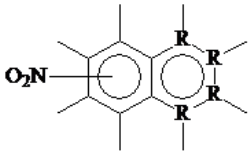


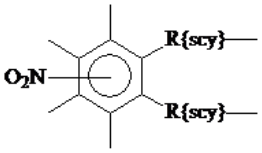
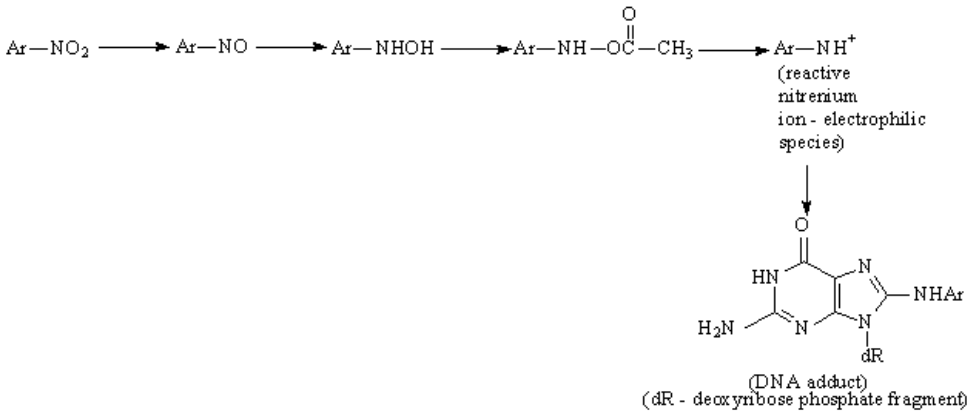
Homolytic

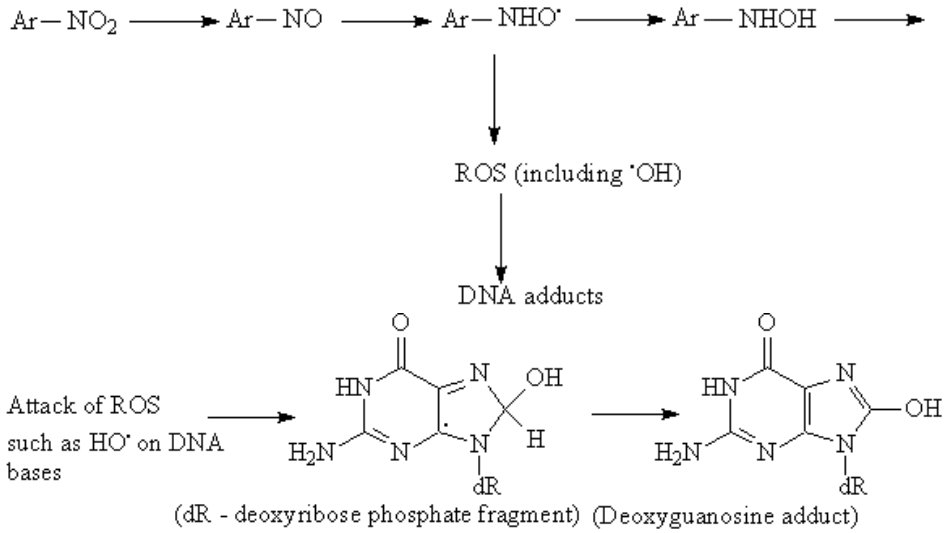


Set of chemicals used for profile development	Nitroaniline Derivatives
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Sabbioni, G., Envir. Health Persp. **102**, Suppl. 6 (1994), 61 – 67.

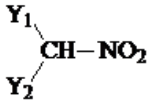
	2. Kalgutkar, A. S., Current Drug Metabol. **6** (2005), 161 – 225. 3. Aiub, Cl. A. Fortes, Chem.-Biol. Interact. **161** (2006), 146 – 154. 4. Einisto, P., Mutat. Res. **259** (1991), 95 – 102. 5. Kovacic, P., Current Med. Chem. **8**, (2001), 773 – 796. 6. Witherell, H. L., Canc. Epidemiol. Biomarkers & Prevention **7** (1998), 91 – 96. 7. Wiseman, H., Biochem. J. 313 (1996), 17 – 29. 8. Purohit, V., Chem. Res. Toxicol. **13**(8) (2000), 673 – 692. 9. Vance, W. A., Environ. Mutagen, **6** (6) (1984), 797 – 811. 10. Y. Lee, Mol. Cells **19**, No. 1 (2005), 114 – 123 (Abstract); http://agris.fao.org/agris-search/search/display.do?f=2006/KR/KR0603.xml;KR2006013346. 11. Shimizu, M., Mutat. Res. **170** (1986), 11 – 22. 12. Assmanna, N., Mutat. Res. **395** (1997), 139 – 144. 13. Garner, R. C., Mutat. Res. **44** (1977), 9 – 19. 14. *Opinion on 4-Nitro-o-Phenylenediamine*, Colipa No. 824, Scientific Committee on Consumer Products, Health&Consumer Protection Directorate-General, EC, December 19, 2006. 15. Chung, K. T., Mutat. Res. **387** (1997), 1 – 16.

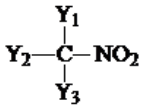
Individual profile/alert	
Name	Fused-Ring Nitroaromatics
Type of profile	Structural alert
Description/applicability domain	**Nitroantraquinones**  **Nitrofluorenes and their heterocyclic analogues**  **Y= C or S(V2) , N(V3) (sp^3)** **Other fused-ring nitroaromatics** 

	R= C or N(number of N is 1 or 2) ; Can't have SO_3H group attached to the ring, bearing NO_2  **R(scy)= C or N(V3) or S(V2) or a combination as part of a fused cyclic fragment**
Mechanism	**Heterolytic Mechanism.** This is the most important mechanism, associated with the bacterial mutagenicity of nitroarenes, and, particularly, the sub-class discussed here. The DNA damage, eliciting bacterial mutagenicity results mainly from covalent adduct formation. It arises from several activated metabolites, including the N-hydroxylamine (proximate mutagenic form) and its O-esterified derivative formed by phase II (O-acetylation, sulfation) enzymatic reaction with the subsequent generation of electrophilic nitrenium ion. The latter species may exert electrophilic attack on DNA bases. (**Nucleophilic attack after reduction and nitrenium ion formation)** **Radical (Homolytic) Mechanism.** This is one of the mechanisms (but not the most important) for eliciting bacterial mutagenicity of nitro compounds. Certain monocyclic and polycyclic aromatic nitro compounds (ArNO2) are implicated in carcinogenesis. Reduction of the nitro to the nitroso intemediate is followed by formation of N-hydroxylamine species and may occur in the prokaryotic Salmonella typhimurium cell. Several transient radical intermediates, including reactive oxygen species (ROS) are formed during this process, and have been found to cause oxidative DNA damage (strand breaks) **(Radical mechanism *via* ROS formation (indirect)**
Heterolytic  **Homolytic**	

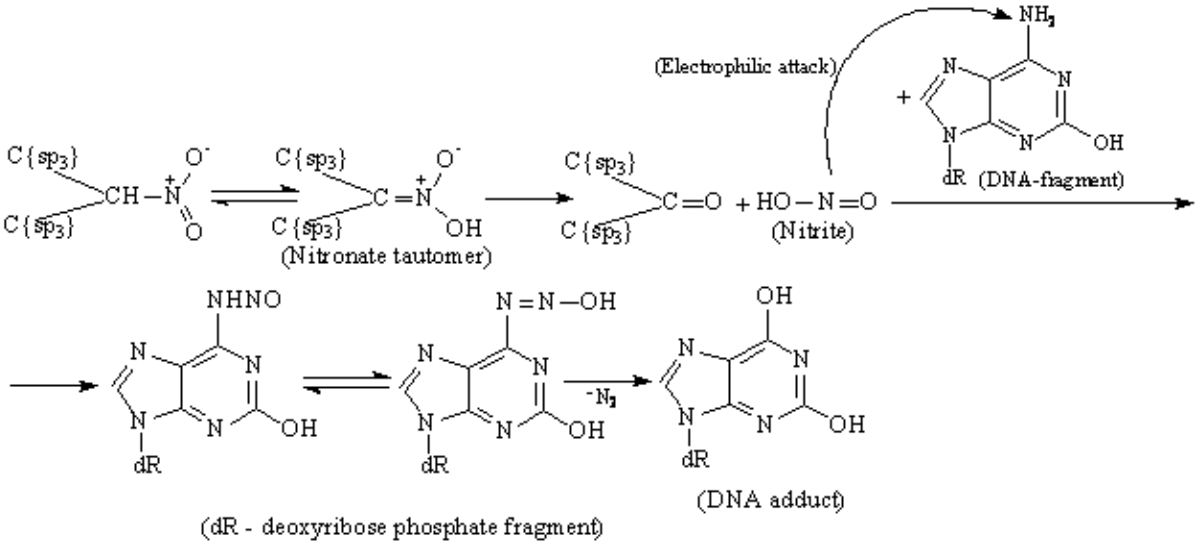


Set of chemicals used for profile development	Fused-Ring Nitroaromatics
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1.Sabbioni, Envir. Health Persp. **102**, Suppl. 6 (1994), 61 – 67. 2.Kalgutkar, Current Drug Metabol. **6** (2005), 161 – 225. 3.Aiub, Chem.-Biol. Interact. **161** (2006), 146 – 154. 4.Einisto, Mutat. Res. **259** (1991), 95 – 102. 5.Kovacic, Current Med. Chem. **8**, (2001), 773 – 796. 6.Witherell, Canc. Epidemiol. Biomarkers & Prevention **7** (1998), 91 – 96. 7.Wiseman, Biochem. J. **313** (1996), 17 – 29. 8.Purohit, Chem. Res. Toxicol. **13**(8) (2000), 673 – 692. 9. Rosenkranz, Mutat. Res. **114** (1983), 217 – 267. 10. Brown, J. P., Mutat. Res. **66** (1979), 9 – 24. 11.Vance, W. A., Environ. Mutag. **6** (1984), 797 – 811.

Individual profile/alert	
Name	Nitroalkanes
Type of profile	Structural alert
Description/applicability domain	**Monoalkanes**  **Y_1- Me or H** **Y_2- Me or CH_2OH or CH_2COOH** **Low Molecular weight germinal Polynitroalkanes**

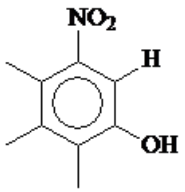
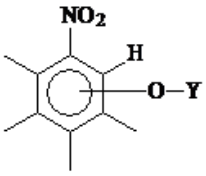
	 **Y_1, Y_2, Y_3 can be NO_2(all) or a combination between $–CH_3$, -H, -NO_2. The number of NO_2 groups to be more than one.**
Mechanism	**Nucleophilic substitution after nitrite formation & Radical mechanism *via* ROS formation (indirect)**

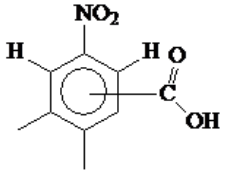
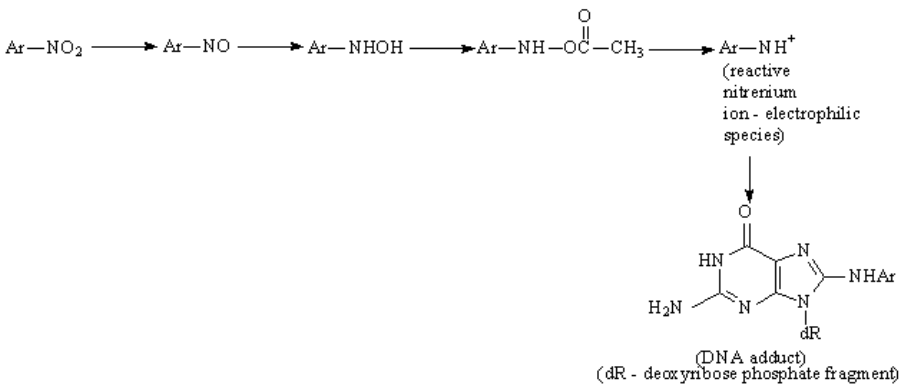
The following possible scheme for *in vitro* biotransformation can be therefore proposed for secondary nitroalkanes has been tested for mutagenic activity in the *Salmonella/mammalian* microsome assay and showed strong *in vitro* genotoxicity. The mutagenicity was independent of an *in vitro* metabolic activation system; therefore, this chemical is regarded as direct-acting mutagen. Tetranitromethane is a potent protein nitrating agent and has been proposed to have role in the deamination of DNA (deamination of cytosine resulting in base mispair). However, there is insufficient information on the precise mechanism of mutagenicity/carcinogenicity of this compound [6, 7]. According to some publications, tetranitromethane is a new type of carcinogen that induces oxidative DNA damage not by itself but *via* modification (nitrosation) of tyrosine residues in proteins, which in turn generates reactive oxygen species (ROS), capable of forming DNA adducts [8].



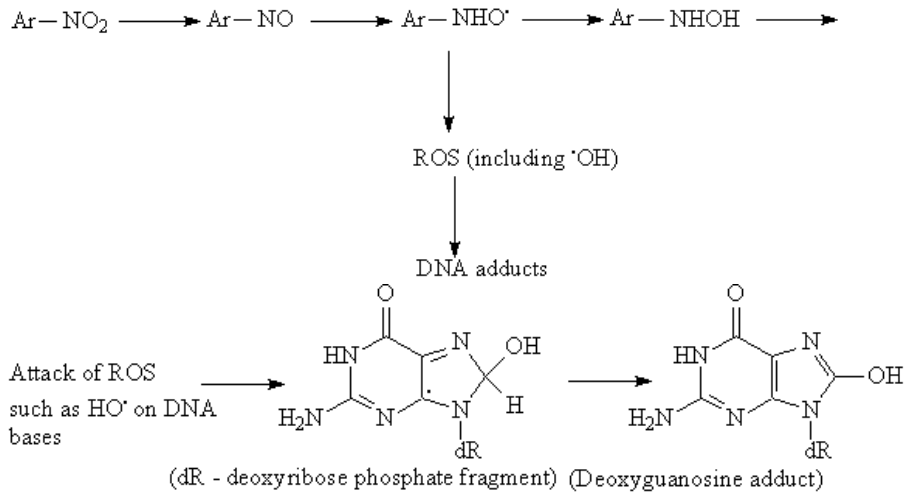
Set of chemicals used for profile development	Nitroalkanes
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Conaway Mutat. Res. **261**(3) (1991), 197 – 207; http://www.ncbi.nlm.nih.gov/pubmed/1719412); DOI: 10.1016/0165-1218(91)90068-w. 2. Dayal, R., Fund. Appl. Toxicol. **13**(2) (1989), 341 – 348; http://www.sciencedirect.com/science/article/pii/0272059089902704; DOI: 10.1016/0272-0590(89)90270-4. 3. Dalke, C., Toxicol. Lett. **61** (2-3), 1992, pp. 149 – 157. 4. *2-Nitropropane*, International Programme on Chemical Safety,

	Environmental Health Criteria 138, World Health Organization, Geneva, 1992; www.inchem.org/documents/ehc/ehc/ehc138.htm. 5. *Ingested Nitrate and Nitrite, and Cyanobacterial Peptide Toxins. 4. Mechanistic and Other Relevant Data*, IARC Monographs on the Evaluation of Carcinogenic Risk to Humans Vol. 94, 2010, p. 281 (Lyon, France); http://monographs.iarc.fr/ENG/Monographs/vol94/mono94.pdf; ISBN-13 (PDF): 978-92-832-1594-3. 6. Wurgler, Mutat. Res. Lett. **244**(1) (1990), 7 – 14. 7. *Toxicology and Carcinogenesis Studies of Tetranitromethane in F344/N Rats and B6C3F1 Mice (Inhalation Studies)*, NTP Technical Report Series No. 386, March 1990, US Dept. of Health and Human Services, Public Health Service, NIH; http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr386.pdf. 8. Murata, M., Chem. Res. Toxicol. **19**(10) (2006), 1379 – 1385. 9. Linhart, I., Chem.-Biol. Interact. **80** (1991), 187 – 210. 10. Sundvall, Mutat. Res. **137** (1984), 71 – 78..

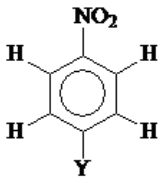
Individual profile/alert	
Name	Nitrophenols, Nitrophenyl Ethers and Nitrobenzoic Acids
Type of profile	Structural alert
Description/applicability domain	**Nitrophenols**  **No more than three substituents** **No -SO_3H and –COO-** **Nitrobenzyl and Nitrobenzyl Halides**  **Y= Me, Et** **No more than three substituents** **No –SO_3H and –COO-** **Nitrophenyl Diazonium Salts and Nitrophenyl**

	 **No more than three substituents** **No –SO_3H and –COO-**
Mechanism	**Heterolytic Mechanism.** This is the most important mechanism, associated with the bacterial mutagenicity of nitroarenes, and, particularly, the sub-class discussed here. The DNA damage, eliciting bacterial mutagenicity results mainly from covalent adduct formation. It arises from several activated metabolites, including the N-hydroxylamine (proximate mutagenic form) and its O-esterified derivative formed by phase II (O-acetylation, sulfation) enzymatic reaction with the subsequent generation of electrophilic nitrenium ion. The latter species may exert electrophilic attack on DNA bases. (**Nucleophilic attack after reduction and nitrenium ion formation)** **Radical (Homolytic) Mechanism.** This is one of the mechanisms (but not the most important) for eliciting bacterial mutagenicity of nitro compounds. Certain monocyclic and polycyclic aromatic nitro compounds (ArNO2) are implicated in carcinogenesis. Reduction of the nitro to the nitroso intemediate is followed by formation of N-hydroxylamine species and may occur in the prokaryotic Salmonella typhimurium cell. Several transient radical intermediates, including reactive oxygen species (ROS) are formed during this process, and have been found to cause oxidative DNA damage (strand breaks) **(Radical mechanism *via* ROS formation (indirect)**
Heterolytic  	

Homolytic

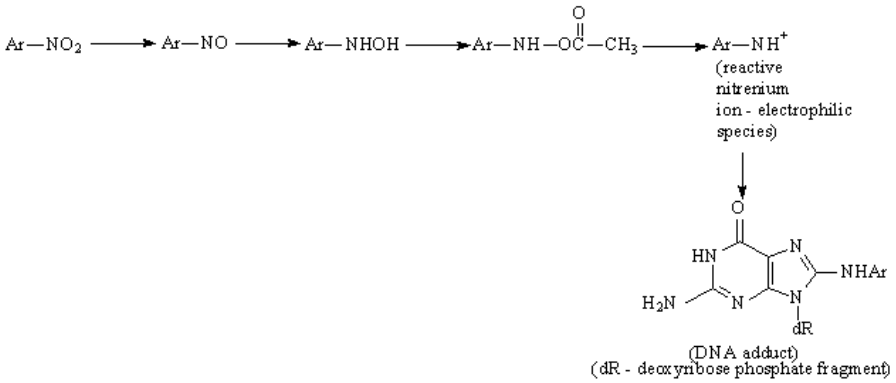


Set of chemicals used for profile development	Nitrophenols, Nitrophenyl Ethers and Nitrobenzoic Acids
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1.Sabbioni, Envir. Health Persp. **102**, Suppl. 6 (1994), 61 – 67. 2.Kalgutkar, Current Drug Metabol. **6** (2005), 161 – 225. 3.Aiub, Chem.-Biol. Interact. **161** (2006), 146 – 154. 4.Einisto, Mutat. Res. **259** (1991), 95 – 102. 5.Kovacic, Current Med. Chem. **8**, (2001), 773 – 796. 6.Witherell, Canc. Epidemiol. Biomarkers & Prevention **7** (1998), 91 – 96. 7.Wiseman, Biochem. J. **313** (1996), 17 – 29. 8.Purohit, Chem. Res. Toxicol. **13**(8) (2000), 673 – 692. 9. Shimizu, Mutat. Res. **170** (1986), 11 – 22. 10. Sundvall, Mutat. Res. **137** (1984), 71 – 78. 11. Mononitrophenols, Concise International Chemical Assessment Document 20, World Health Organization, Geneva 2000; http://www.who.int/ipcs/publications/cicad/en/cicad20.pdf.

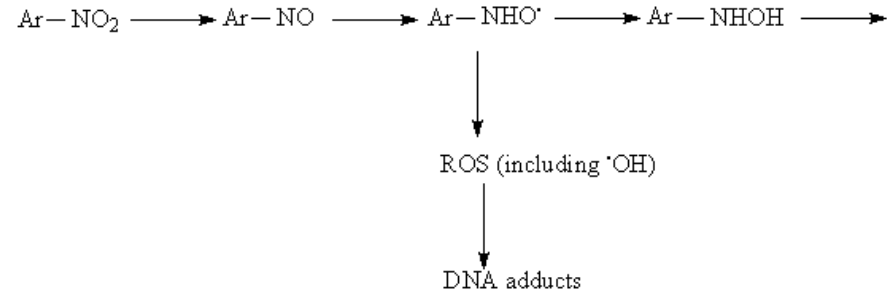
Individual profile/alert	
Name	p-Subtituted Mononitrobenzenes
Type of profile	Structural alert
Description/applicability domain	 **Y= Any Carbon(sp^3) or Aliphatic Carbon(sp^2)**

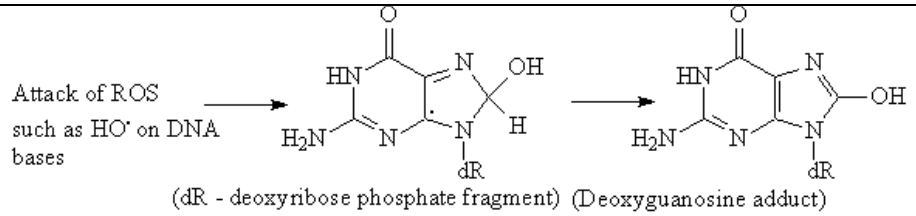
Mechanism	**Heterolytic Mechanism.** This is the most important mechanism, associated with the bacterial mutagenicity of nitroarenes, and, particularly, the sub-class discussed here. The DNA damage, eliciting bacterial mutagenicity results mainly from covalent adduct formation. It arises from several activated metabolites, including the N-hydroxylamine (proximate mutagenic form) and its O-esterified derivative formed by phase II (O-acetylation, sulfation) enzymatic reaction with the subsequent generation of electrophilic nitrenium ion. The latter species may exert electrophilic attack on DNA bases. (**Nucleophilic attack after reduction and nitrenium ion formation)** **Radical (Homolytic) Mechanism.** This is one of the mechanisms (but not the most important) for eliciting bacterial mutagenicity of nitro compounds. Certain monocyclic and polycyclic aromatic nitro compounds (ArNO2) are implicated in carcinogenesis. Reduction of the nitro to the nitroso intemediate is followed by formation of N-hydroxylamine species and may occur in the prokaryotic Salmonella typhimurium cell. Several transient radical intermediates, including reactive oxygen species (ROS) are formed during this process, and have been found to cause oxidative DNA damage (strand breaks) **(Radical mechanism *via* ROS formation (indirect)**

Heterolytic

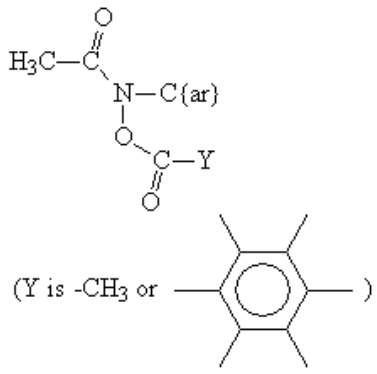


Homolytic

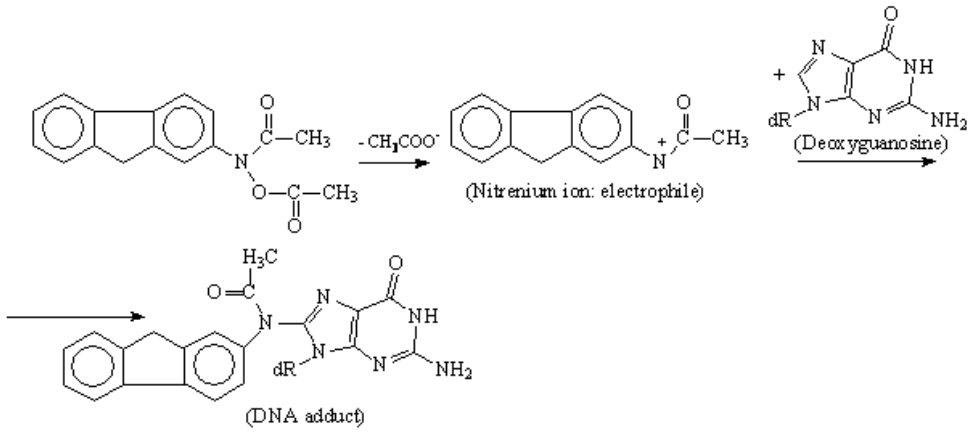




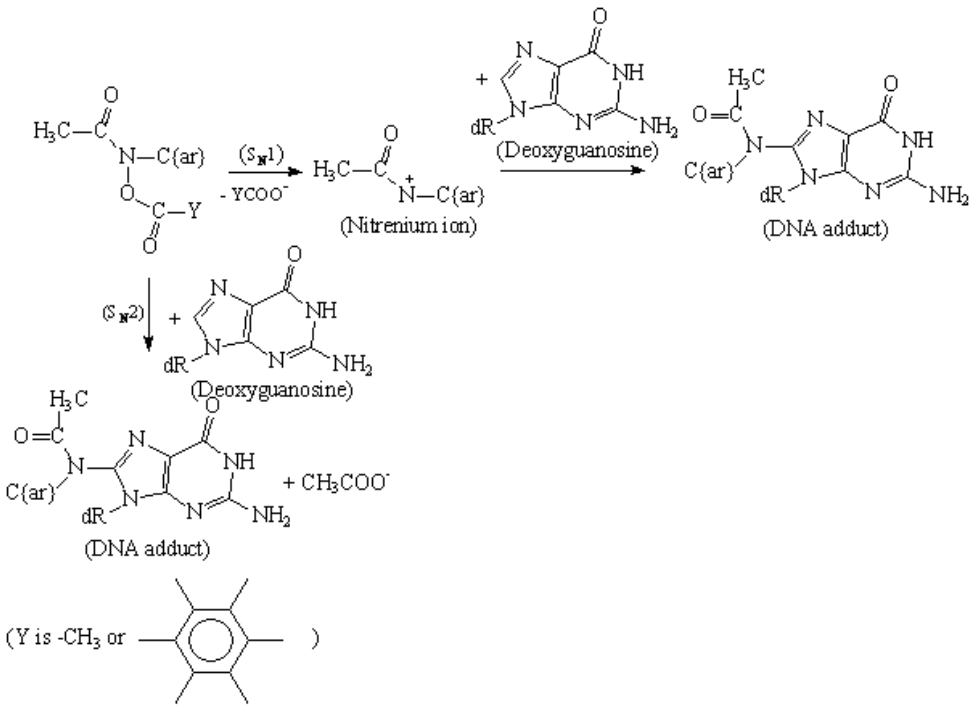
Set of chemicals used for profile development	p-Substituted Mononitrobenzenes
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1.Sabbioni, Envir. Health Persp. **102**, Suppl. 6 (1994), 61 – 67. 2.Kalgutkar, Current Drug Metabol. **6** (2005), 161 – 225. 3.Aiub, Chem.-Biol. Interact. **161** (2006), 146 – 154. 4.Einisto, Mutat. Res. **259** (1991), 95 – 102. 5.Kovacic, Current Med. Chem. **8**, (2001), 773 – 796. 6.Witherell, Canc. Epidemiol. Biomarkers & Prevention **7** (1998), 91 – 96. 7.Wiseman, Biochem. J. **313** (1996), 17 – 29. 8.Purohit, Chem. Res. Toxicol. **13**(8) (2000), 673 – 692. 9. Shimizu, M., E. Yano, Mutat. Res. **170** (1986), 11 – 22; *Chemical Carcinogenesis Research Information System*, TOXNET, US National Library of Medicine; http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?CCRIS.

Individual profile/alert	
Name	N-Aryl-N-Acetoxy(Benzoyloxy) Acetamides
Type of profile	Structural alert
Description/applicability domain	
Mechanism	**S_N2 or S_N1 reaction at nitrogen atom bound to a good leaving group or on nitrenium ion**
The lipid-soluble N-acetoxy and N-benzoyloxy-derivatives of the compound N-2-fluorenylacetamide as well as the N-benzoyloxy derivative of N-methyl-4-aminoazobenzene, and the N-acetoxy derivatives of N-4-stilbenylacetamide , N-4-biphenylylacetamide, and N-2-phenanthrylacetamide are each more carcinogenic at the sites of subcutaneous injection than the correspondinng parent compounds. These acetoxyesters are also much more reactive with nucleophiles such as nitrogen	

atoms in DNA bases than the corresponding N-hydroxylamine precursors. The nature of the aryl group, however, has a pronounced effect on both the reactivity and carcinogenicity of the hydroxamic acids and their esters. In the presence of nucleophiles that are less basic than acetate ion, the 2-fluorenyl and 4-stilbenyl-N-acetoxyacetamides reacted *via* unimolecular ionization (S_N1 mechanism), and the initial attack on the DNA bases occurs at their nitrogen atoms, followed by rearrangement. The unimolecular mechanistic scheme is shown below in Scheme 1 [1]:

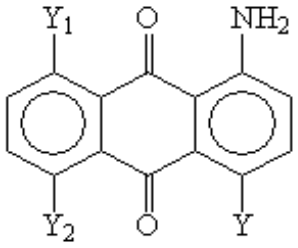
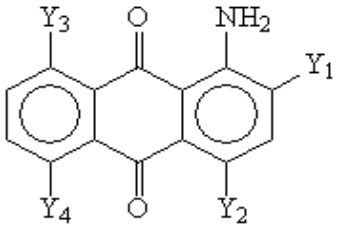


The general scheme for such interactions with DNA fragments could be outlined as follows:



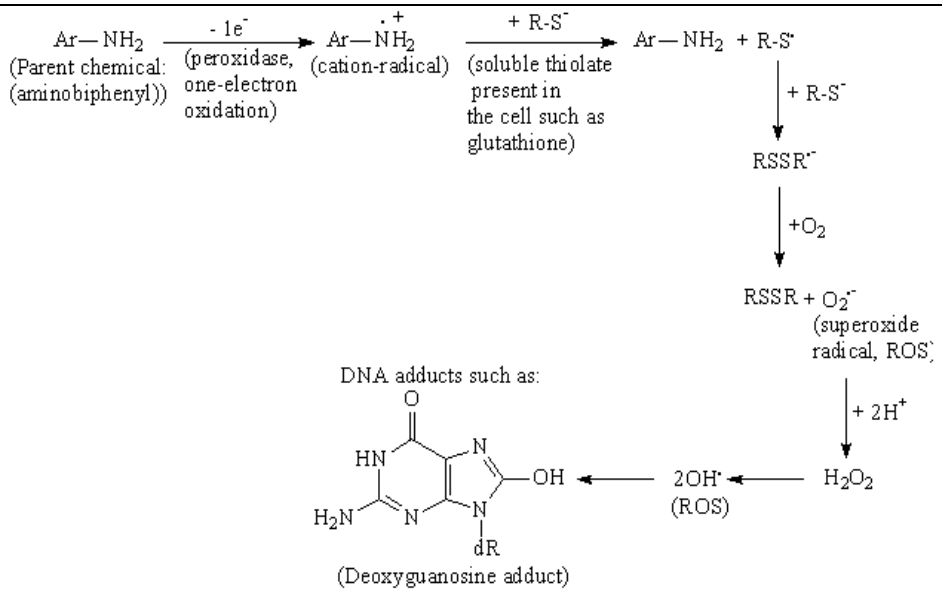
Scheme 1

Set of chemicals used for profile development	N-Aryl-N-Acetoxy(Benzoyloxy) Acetamides
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Scribner, Canc. Res. **30** (1970), 1570 – 1579. 2. Swaminathan, Canc. Res. **52** (1992), 3286 – 3294.

Individual profile/alert	
Name	Amino Anthraquinones
Type of profile	Structural alert
Description/applicability domain	 (Y can be -OH or -NH_2; Y_1, Y_2 can be -OH, -NH_2 or -H)  (Y_1 can be -Cl, -Br, -COOH, -OH or -NH_2); Y_2 can be Cl or Br or -H; Y_3, Y_4 can be -OH, -NH_2 or -H)
Mechanism	**S_N1 Nucleophilic attack after metabolic nitrenium ion formation, Non-covalent interaction DNA intercalation & Radical ROS formation (indirect)**

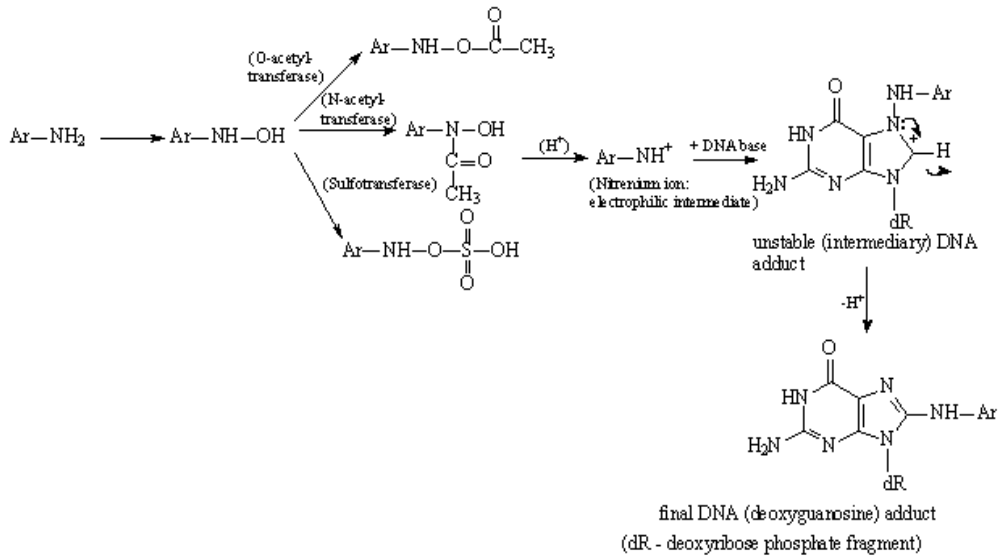
DNA intercalation: The presence of some electron-donating substituents with +M-effect can contribute to the direct mutagenicity of such chemicals, since the benzene rings become more electron-rich and this enhances the non-covalent interaction of the parent chemicals with DNA. Particularly important in this respect are substituents such as –NH_2 and –OH located at *o*- or *p*-postions towards each other. Conjugation effects, planarity and the location of at least one of the primary amino groups at position 1 are also contributing factors

Endogenous generation of reactive oxygen species (ROS). Peroxidase enzymes might be present in *Salmonella typhimurium* bacterial strains, which are associated with endogenous generation of oxygen intermediates [7]. Generally, genotoxicity by oxygen intermediates may be caused by oxidative stress as a result of intracellular species, which can undergo one-electron oxidation-reduction reactions catalyzed by peroxidases to radical species. The latter interact with oxygen to form reactive oxygen species (ROS), which can attack the biological macromolecules such as DNA causing genotoxicity. Such processes can be mediated by thiols and/or glutathione present in the cells shown below in Scheme 1 [8, 9]:



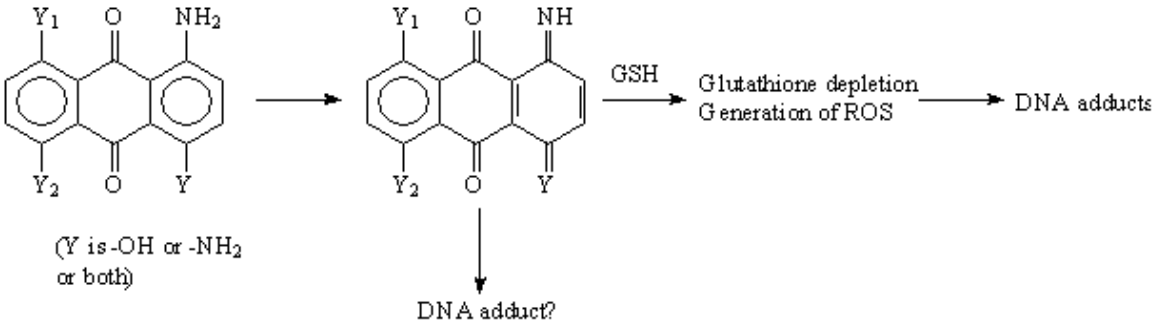
Scheme 1

Mutagenicity after metabolic activation with S9 mix. There is strong evidence that aromatic amines, including aminoanthraquinone derivatives in many cases require metabolic activation with the external microsomal S9 system for eliciting mutagenicity and carcinogenicity. According to an excellent review on the bioactivation pathways of organic functional groups, the obligatory step in the bioactivation of all aniline derivatives involves enzymatic N-hydroxylation on the primary amine nitrogen, leading to the formation of *N-hydroxylamine* intermediate. These reactive N-hydroxylamine derivatives (metabolites) can undergo phase II conjugation, to generate the more reactive N-O sulfate and/or N-O acetyl conjugates. The excellent leaving group capability of sulfonyloxy- and acetoxy-functionalities in these conjugates is believed to lead to a highly reactive *nitrenium ion*. The nitrenium ion electrophilic species may readily bind covalently to cellular DNA and RNA [10]. The principal *in vitro* metabolic pathway causing mutagenicity of aromatic amines is therefore associated with metabolic activation induced by interactions with the CYP450 isoenzyme CYP1A2, and can be outlined as follows shown below in Scheme 2[11]:



Scheme 2

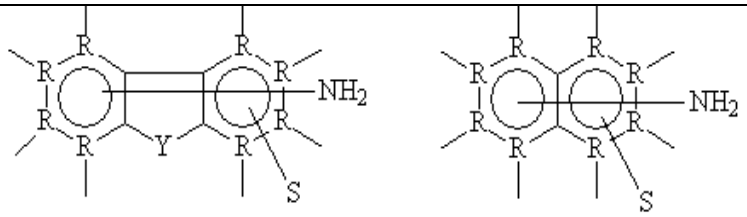
Not only is nitrenium ion chemistry implicated in the DNA damage. For some specific anthraquinone derivatives with electron-donating substituents mutually located at *p*- or *o*-positions, reactions associated with the formation of quinones, quinone imines or other quinoid structures could be involved in the elucidation of the overall mechanistic scheme of bioactivation shown below in Scheme 3 [12]:



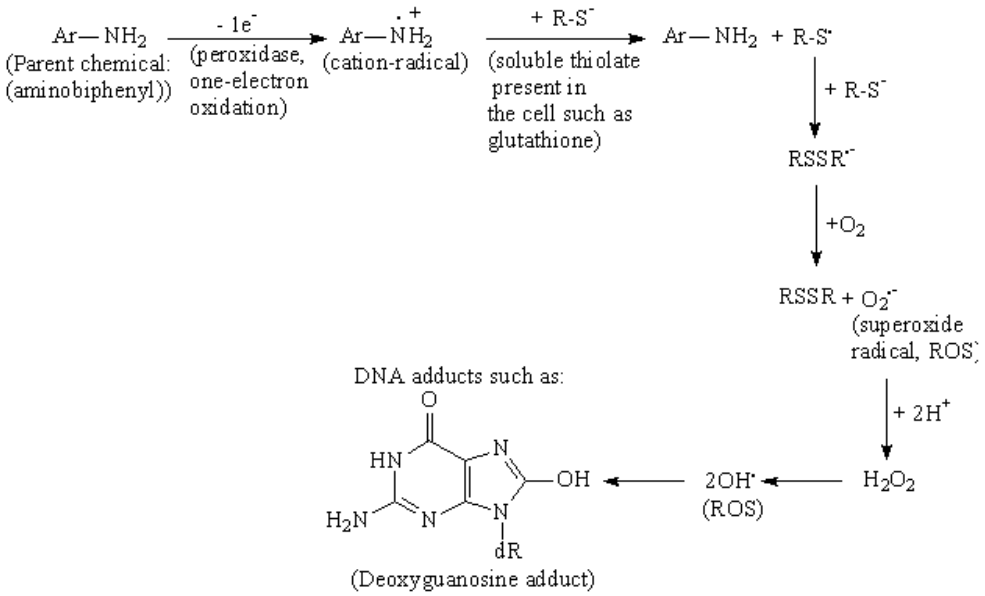
Scheme 3

Set of chemicals used for profile development	Amino Anthraquinones
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1.Zeiger, E., Canc. Res. **47** (1987), 1287 – 1296. 2.Venturini, S., Mutat. Res. **68** (1979), 307 – 312. 3. Double, J. Pharm. Pharmac. **28** (1976), 166 – 169. 4. Gouda, Turk. J. Chem. **34** (2010), 651 – 709. 5. Brock, Mutagen. **6**(1) (1991), 35 – 46. 6. *Chemical Carcinogenesis Research Information System (CCRIS)*; http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?CCRIS. 7. Lang, Mutat. Res. **191** (1987), 139 – 143. 8. Subrahmany, Chem.-Biol. Interactions **56** (1985), 185 – 199. 9. Makena, Environ. Molec. Mutagenesis **48** (2007), 404 – 413. 10. Kalgutkar, Curr. Drug Metabol. **6**(3), 2005, 161 – 225. 11. Shamovsky, JACS **133** (2011), 16168 – 16185. 12. Skipper, Carcinog. **31**(10) (2010), 50 – 58.

Individual profile/alert	
Name	Fused ring Primary Aromatic Amines
Type of profile	Structural alert
Description/applicability domain	

	 (S can be -C{sp3}, no more than three C{sp3}; -O-C{sp3}in alkyl chain, no more than three C{sp3}; -NH- or -H or -OH or $-NO_2$; S can be attached anywhere to an aromatic ring; Y is CH_2 or -NH; R can be C{ar} only or combinations of C{ar} and N{ar}; no more than two N{ar}in a molecular structure). No electron-withdrawing substituents attached such as $-SO_3H$, CN, C=O, $-CF_3$, $-SO_2$, N{V3}{sp2}, halogen (F, Cl, Br). No more than four fused rings)
Mechanism	**S_N1 Nucleophilic attack after metabolic nitrenium ion formation, Radical ROS generation (indirect) & Non-covalent interactions DNA intercalation**

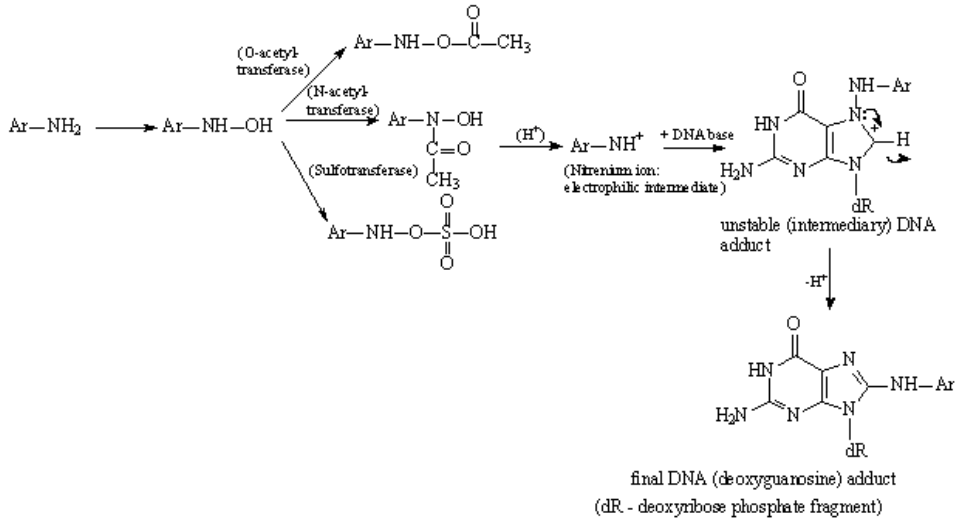
It is expertly assumed that the presence of electron-donating substituents with either +I or +M-effects, together with the planar structure and conjugation effects may determine the positive mutagenicity of some polycyclic aromatic amines as parent chemicals. In addition, endogenous generation of reactive oxygen species can be assumed, due to the presence of peroxidase enzymes in bacterial cells, and this process can be mediated by thiols shown below in Scheme 1 [5, 6]:



Scheme 1

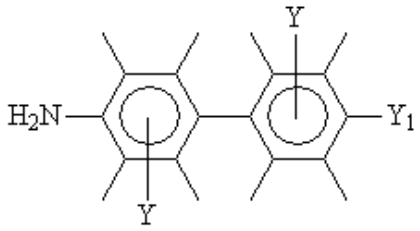
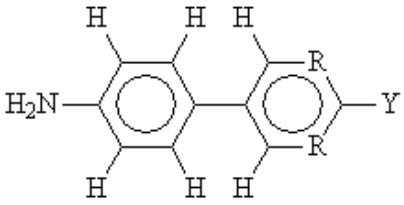
For all sub-classes of primary aromatic amines, including the polycyclic ones, there is strong evidence that, in many cases, metabolic activation with the external microsomal S9 system is required for eliciting mutagenicity and carcinogenicity. According to an excellent review on the bioactivation pathways of organic functional groups, the obligatory step in the bioactivation of all aniline derivatives involves enzymatic N-hydroxylation on the primary amine nitrogen, leading to the formation of *N-hydroxylamine* intermediate. These reactive N-hydroxylamine derivatives (metabolites) can undergo phase II conjugation, to generate the more reactive N-O sulfate and/or N-O acetyl conjugates. The excellent leaving group capability of sulfonyloxy- and acetoxy-functionalities

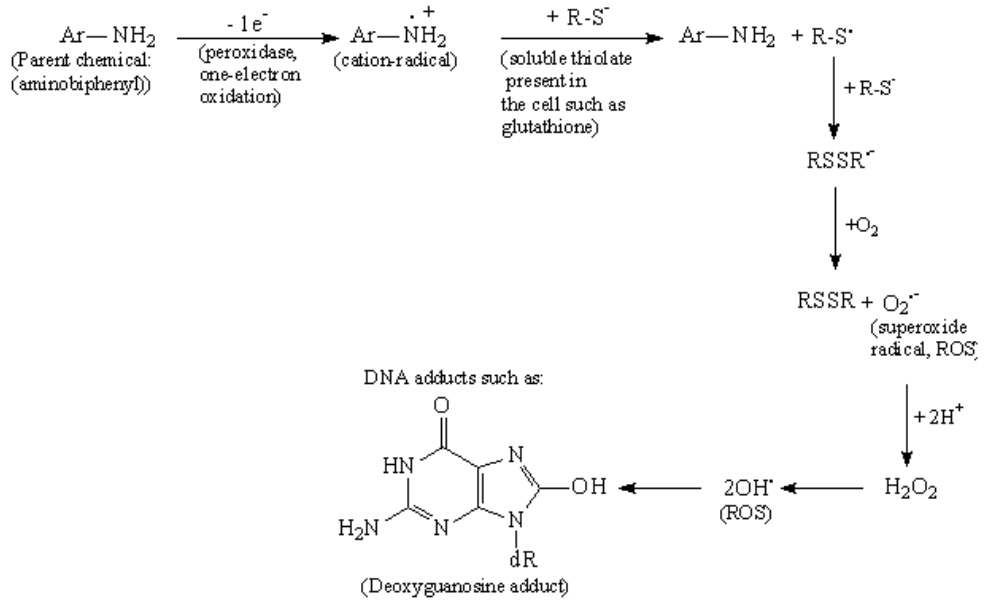
in these conjugates is believed to lead to a highly reactive *nitrenium ion*. The nitrenium ion electrophilic species may readily bind covalently to cellular DNA and RNA [9]. The principal *in vitro* metabolic pathway causing mutagenicity of aromatic amines is therefore associated with metabolic activation induced by interactions with the CYP450 isoenzyme CYP1A2, and can be outlined as follows shown below in Scheme 2 [10]:



Scheme 2

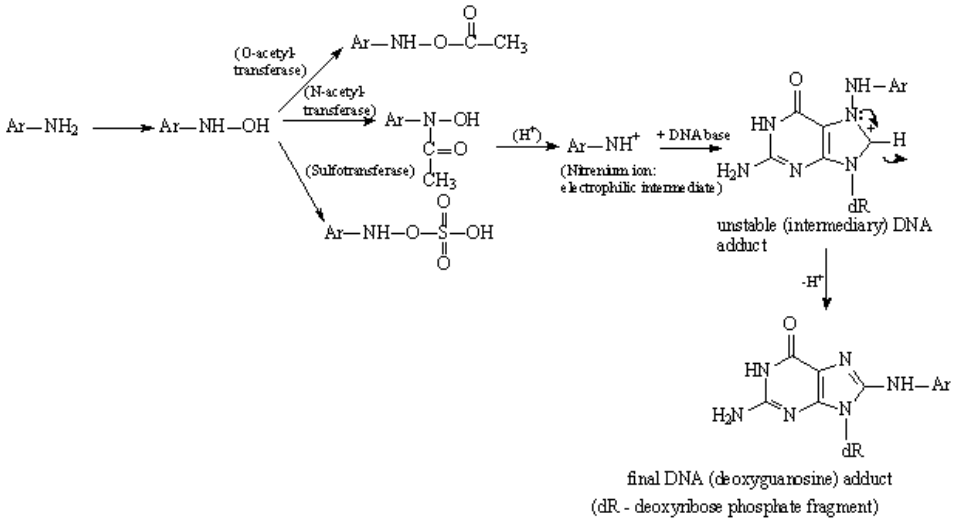
Set of chemicals used for profile development	Fused-Ring Primary Aromatic Amines
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Double, J. Pharm. Pharmac. **28** (1976), 166 – 169. 2. Shapiro, Chem. Res. Toxicol. **11** (1998), 335 – 341. 3. *Chemical Carcinogenesis Research Information System (CCRIS)*; http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?CCRIS). 4. Hoffman, Chem. Res. Toxicol. **10**(4) (1997), 347 – 359). 5. Subrahmany, V. V., Chem.-Biol. Interactions **56** (1985), 185 – 199. 6. Makena, Environ. Molec. Mutagenesis **48** (2007), 404 – 413. 7. Guerin, Environ. Res. **23** (1980), 42 – 53). 8. Chung, K. T., App. Environ. Microbiol. **42**(4) (1981), 641 – 648. 9. Kalgutkar, Curr. Drug Metabol. **6**(3), 2005, 161 – 225. 10. Shamovsky, JACS **133** (2011), 16168 – 16185 11. Glatt, H., FASEB J. **11**(5) (1997), 314 – 321. 12. Chung, Mutat. Res. 387 (1) 1997, 1 – 16. 13. Franke, R. , Carcinogenesis **22**(9) (2001), 1561. 14. Fu, Mutat. Res. **94** (1982), 13 – 21.

Individual profile/alert	
Name	p-Aminobiphenyl Analogs
Type of profile	Structural alert
Description/applicability domain	 (Y can be F, Cl, Br, or -OCH_3, or -CH_3 or -NO_2; no other types of substituents; Y_1 can be -NH_2 or *p*-$C_6H_4NH_2$; no more than totally three substituents on each benzene ring; single (non-fused) benzene rings only)  (Y can be -NH_2 or *p*-$C_6H_4NH_2$; R can be C and N or both N)
Mechanism	**S_N1 Nucleophilic attack after nitrenium ion formation & Radical ROS generation (indirect)**
If the presence of endogenous peroxidase enzymes in the "classical" *Salmonella typhimurium* strains is assumed, the following mechanistic scheme involving the formation of reactive oxygen species (ROS) could explain the observed positive *in vitro* bacterial mutagenicity results for aminobiphenyls as parent chemicals shown below in Scheme 1:	



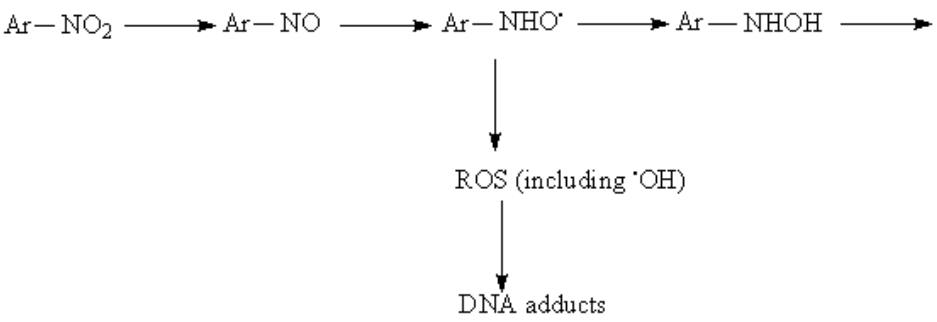
Scheme 1

However, there is strong evidence that aromatic amines, including aminobiphenyls in most cases require metabolic activation with the external microsomal S9 system for eliciting mutagenicity and carcinogenicity. According to an excellent review on the bioactivation pathways of organic functional groups, the obligatory step in the bioactivation of all aniline derivatives involves enzymatic N-hydroxylation on the primary amine nitrogen, leading to the formation of *N-hydroxylamine* intermediate. These reactive N-hydroxylamine derivatives (metabolites) can undergo phase II conjugation, to generate the more reactive N-O sulfate and/or N-O acetyl conjugates. The excellent leaving group capability of sulfonyloxy- and acetoxy-functionalities in these conjugates is believed to lead to a highly reactive *nitrenium ion*. The nitrenium ion electrophilic species may readily bind covalently to cellular DNA and RNA [5]. The principal *in vitro* metabolic pathway causing mutagenicity of aromatic amines is thefefore associated with metabolic activation induced by interactions with the CYP450 isoenzyme CYP1A2, and can be outlined as follows shown below in Scheme 2 [6]:



Scheme 2

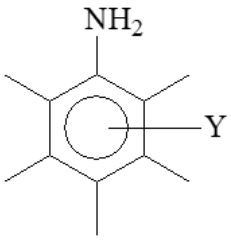
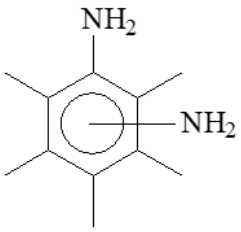
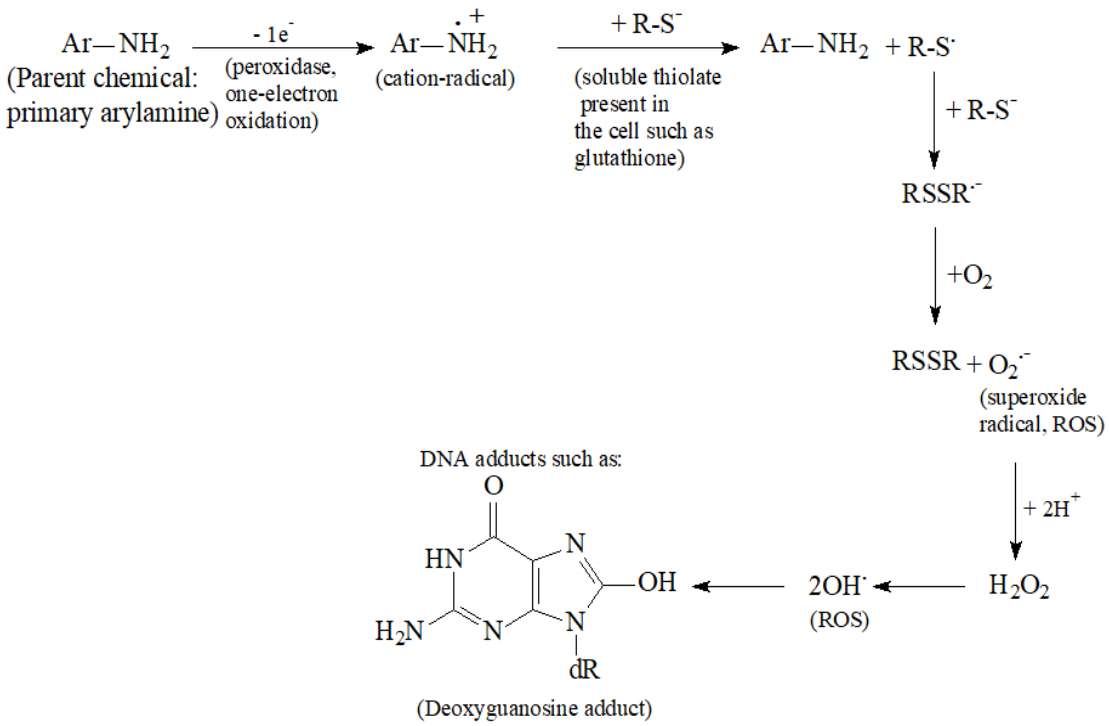
Reduction of the nitro group to nitroso intermediate is followed by formation of N-hydroxylamine species, and may occur endogenously by the bacterial nitroreductase in the prokaryotic *Salmonella typhimurium* cell. As a result, from the generation of reactive radical species such as $ArNHO^{\cdot}$, an additional formation of ROS such as $O_2^{\cdot-}$ and/or $HO^{\cdot}$ occurs. The hydroxyl radical, for example, is DNA-reactive and adducts, involving pyrimidine and purine nucleoside bases can be formed. The 8-hydroxyguanine adduct is one of the most mutagenic lesions so far discovered, which can induce DNA strands breaks, etc. Shown below in Scheme 3 [15, 16]:

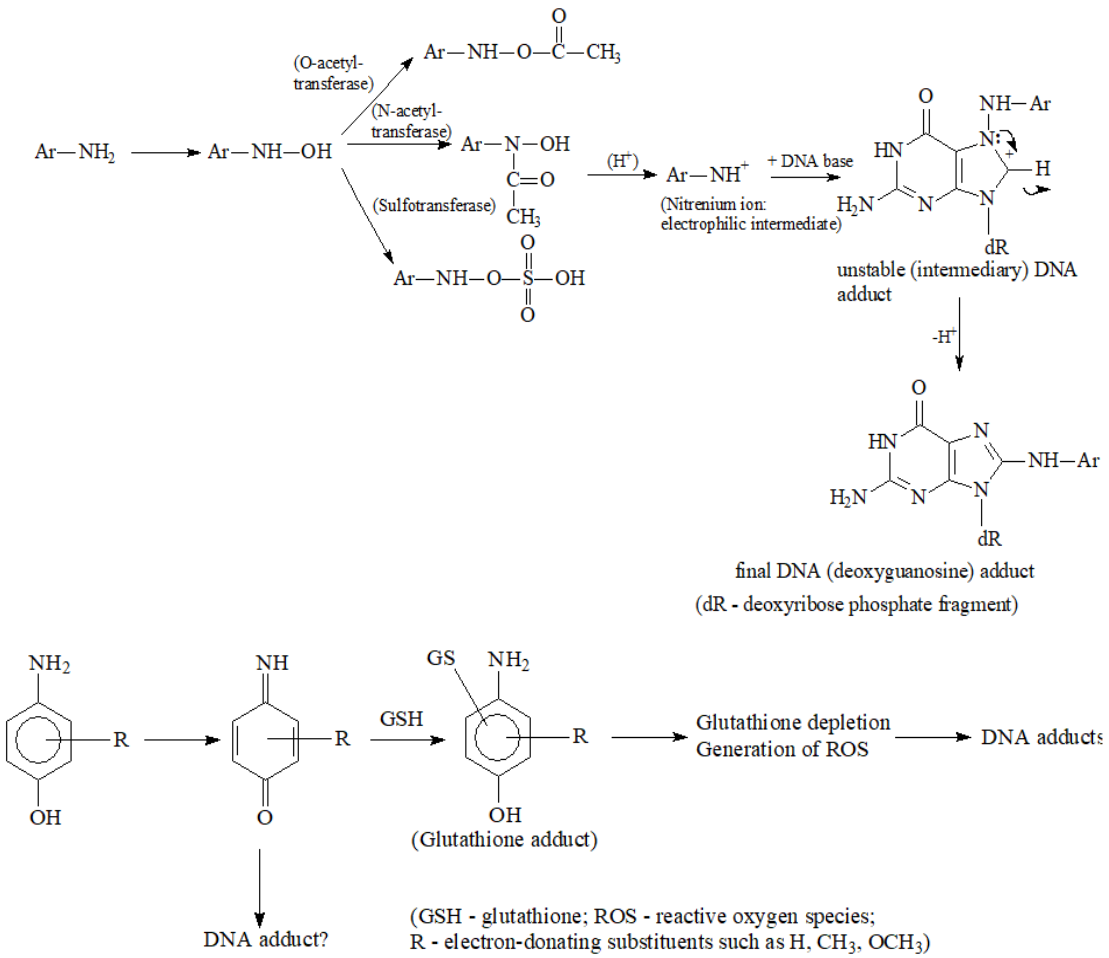


Scheme 3

Set of chemicals used for profile development	p-Aminobiphenyl Analogs
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Savard, Carcinnog. **7** (1986), 1239 – 1241. 2. Lang, Mutat. Res. **191** (1987), 139 – 143. 3. Subrahmany, Chem.-Biol. Interactions **56** (1985), 185 – 199. 4. Makena, Environ. Molec. Mutagenesis **48** (2007), 404 – 413. 5. Kalgutkar, Curr. Drug Metabol. **6**(3), 2005, 161 – 225. 6. Shamovsky, JACS **133** (2011), 16168 – 16185. 7. Humphreys, Proc. Natl. Acad. Sci USA, **89** (1992), 8278 – 8282. 8. Reid, Environ. Mutag. **6** (1984), 145 – 151. 9. Ashby, Mutat. Res. **257** (1991), 229 – 306. 10. Sokolowska, Dyes and Pigments **48** (2001), 15 – 27. 11. El-Bayoumy, Mutat. Res. 90 (1981), 345 – 354. 12. Sinsheimer, Mutat. Res. **268** (1992), 255 – 264. 13. Chung, Toxicol. Sci **56** (2000), 351 – 356. 14. Ioannides, Carcinog. **10**(8) (1989), 1403 – 1407 (Abstract); http://www.ncbi.nlm.nih.gov/pubmed/2665965. 15. Witherell, Canc. Epidemiol. Biomarkers & Prevention **7** (1998), 91 – 96. 16. Wiseman, Biochem. J. 313 (1996), 17 – 29. 17. You, Mutat. Res. 319 (1993), 19 – 30.

Individual profile/alert	
Name	Single-Ring Substituted Primary Aromatic Amines
Type of profile	Structural alert
Description/applicabilit	

y domain	 (Y can be N{V3}, C{sp3}, O-C{sp3}; No more than four substituents; Single-ring aromatic system; Total "masks": -SO_3H and aniline $C_6H_5NH_2$  (No more than two -NH_2 groups)
Mechanism	**S_N1 Nucleophilic attack after nitrenium ion formation & Radical ROS generation (indirect)**
 	



Set of chemicals used for profile development	Single-Ring Substituted Primary Aromatic Amines
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Ames, Br. N., H. O. Kammen, E. Yamasaki, *Hair Dyes Are Mutagenic: Identification of a Variety of Mutagenic Ingredients*, Proc. Nat. Acad. Sci USA **72**(6) (1975), 2423 – 2427. 2. Garner, R. C., C. A. Nutman, *Testing of Some Azo Dyes and Their Reduction Products for Mutagenicity Using Salmonella Typhimurium TA 1538*, Mutat. Res. **44** (1977), 9 – 19. 3. Zimmer, D., J. Mazurek, G. Petzold, B. K. Bhuyan, *Bacterial Mutagenicity and Mammalian Cell Damage by Several Substituted Anilines*, Mutat. Res. **77** (1980), 317 – 326. 4. Thompson, Chr. Z., L. E. Hill, J. K. Epp, G. S. Probst, *The Induction of Bacterial Mutation and Hepatocyte Unscheduled DNA Synthesis by Monosubstituted Anilines*, Environ. Mutag. **5** (1983), 803 – 811. 5. Ashby, J., R. W. Tennant, *Definitive Relationships Among Chemical Structure, Carcinogenicity and Mutagenicity for 301 Chemicals Tested by the US NTP*, Mutat. Res. **257** (1991), 229 – 306. 6. Chung, K. T., L. Kirkovsky, A. Kirkovsky, W. P. Purcell, *Review of Mutagenicity of Monocyclic Aromatic Amines: Structure-Activity Relationships*, Mutat. Res. **387** (1997), 1 – 16. 7. Kranendonk, M., J. N. M. Commandeur, A. Laires, J. Rueff, N. P. E.

Vermeulen, *Characterization of Enzyme Activities and Cofactors Involved in Bioactivation and Bioinactivation of Chemical Carcinogens in the Tester Strains Escherichia coli K12 MX100 and Salmonella typhimurium LT2 TA100*, Mutag. **12**(4) (1997), 245 – 254.
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10. Makena, P. S., K. T. Chung. *Evidence that 4-Aminobiphenyl, Benzidine and Benzidine Congeners Produce Genotoxicity Through Reactive Oxygen Species*, Environ. Molec. Mutagenesis **48** (2007), 404 – 413.
11. Kalgutkar, A. S., I. Gardner, R. S. Obach, Chr. I. Shaffer, E. Callegari, K. R. Henne, A. E. Mutlib, D. K. Dalvie, J. S. Lee, Y. Nakai, J. P. O,Donnell, J. Boer, Sh. P. Harriman, *A Comprehensive Listing of Bioactivation Pathways of Organic Functional Groups*, Curr. Drug Metabol. **6**(3), 2005, 161 – 225.
12. Shamovsky, I., L. Ripa, L. Borjesson, Chr. Mee, B. Norden, P. Hansen, C. Hasselgren, M. O,Donovan, P. Sjo, *Explanation for Main Features of Structure-Genotoxicity Relationships of Aromatic Amines by Theoretical Studies of Their Activation Pathways in CYP1A2*, JACS **133** (2011), 16168 – 16185.
13. Humphreys, W. G., F. F. Kadlubar, F. Peter Guengerich, *Mechanism of C8 Alkylation of Guanine Residues by Activated Arylamines: Evidence of Initial Adduct Formation at the N7 Position*, Proc. Natl. Acad. Sci USA, **89** (1992), 8278 – 8282.
14. Skipper, P. L., M. Y. Kim, H. L. P. Sun, G. N. Wogan, St. R. Tannenbaum, *Monocyclic Aromatic Amines as Potential Human Carcinogens: Old is New Again*, Carcinog. **31**(10) (2010), 50 – 58.
15. *Nitrenium Ions*. Kerdar, R. S., D. Dehner, D. Wild, Reactivity and Genotoxicity of Arylnitrenium Ions in Bacterial and Mammalian Cells, Toxicol. Lett. 67(1-3) (1993), 73 – 85
16. Guengerich, F. P., A. Parikh, E. F. Johnson, T. H. Richardson, C. von Wachenfeldt, J. Cosme, Fr. Jung, C. P. Strassburg, M. P. Mannis, R. H. Tukey, M. Prichard, S. Fournel-Gigleux, Br. Burchell, *Heterologous Expression of Human Drug-Metabolizing Enzymes*, Drug Metabol. Dispos. **25**(11) (1997), 1234 – 1241.
17. Glatt, H., W. Meini, *Use of Genetically Manipulated Salmonella typhimurium Strains to Evaluate the Role of Sulfotransferases and Acetyltransferases in Nitrofen Mutagenicity*, Carcinogenesis **25**(5) (2004), 779 – 786.
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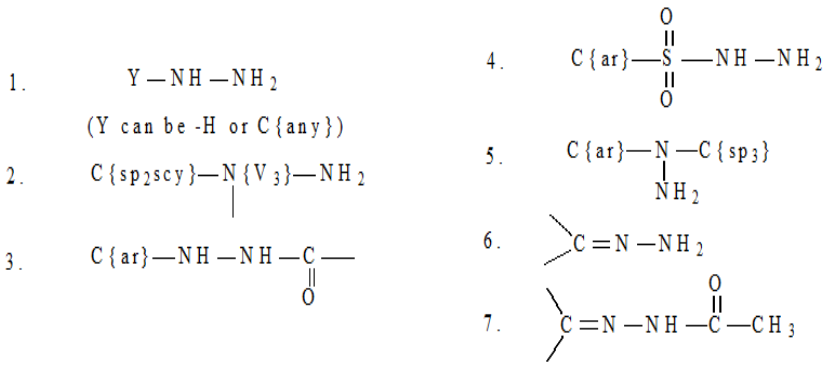
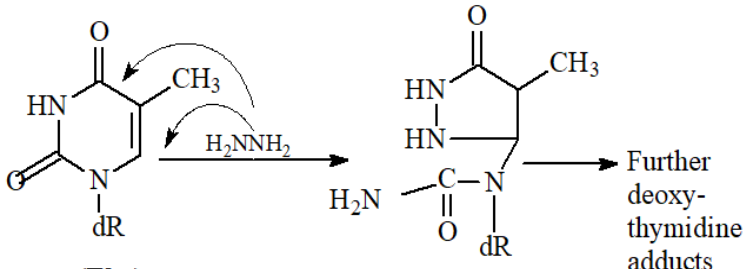
19. Beland, FR., W. B. Melchior Jr., L. L. G. Mourato, M. A. Santos, M. M. Marques, *Arylamine-DNA Adduct Conformation in Relation to Mutagenesis*, Mutat. Res. **376** (1997),13 – 19.
20. NTP Results Report: Results, Status and Publication Information of All NTP Chemicals Produced from Chemtrack System (08/10/00).
21. *3,4-Dichloroaniline*, The MAK Collection for Occupational Health and Safety, 19 June 2013;

	http://onlinelibrary.wiley.com/doi/10.1002/3527600418.mb9576e4013/pdf.

Individual profile/alert	
Name	Hydrazine Derivatives
Type of profile	Structural alert
Description/applicability domain	
Mechanism	**Radical ROS generation (indirect), A_N2 Nucleophilic addition reaction with cycloisomerization & S_N2 Direct nucleophilic attack on diazonium cation**

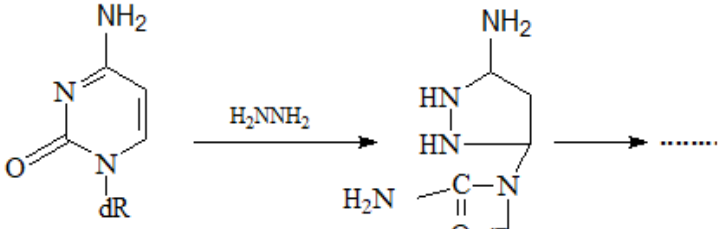
The mechanism of the direct formation of the initial DNA adduct with hydrazine is complex, accompanied by an array of DNA adducts [3]:



(Thy)

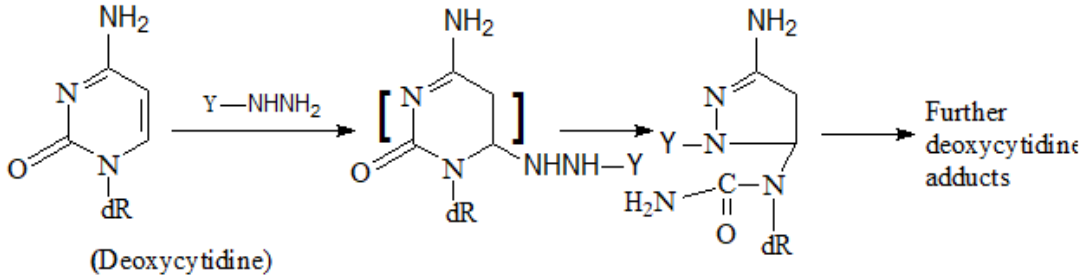
(dR - deoxyribose phosphate fragment)

Similar mechanism has been proposed elsewhere, as illustrated by the formation of adduct(s) with the cytidine fragment of DNA [4]. According to the authors, the initial attack of hydrazine is likely to be predominantly at C6 of the pyrimidine ring, followed by ring closure at C4 (cycloisomerization). The resulting intermediates are substituted dihydropyrazoles, which undergo further chemical transformations with formation of other types of adducts:



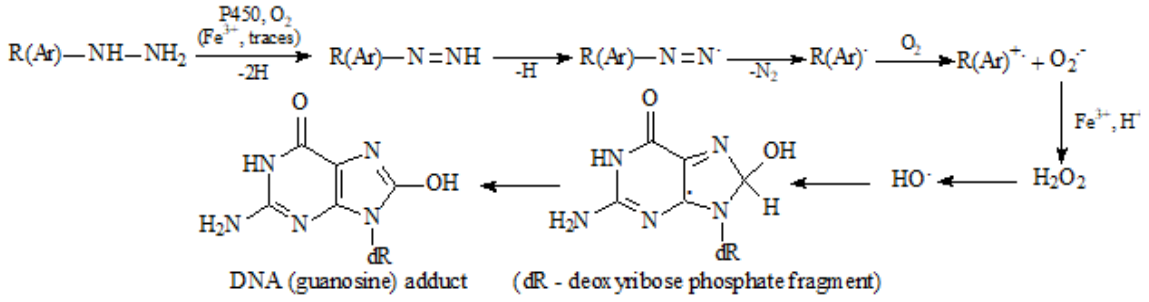
(Deoxycytidine)
(dR - deoxyribose phosphate fragment)

On the basis of the above data, a more general mechanism for the formation of initial adducts with pyrimidine bases of DNA can be expertly suggested:



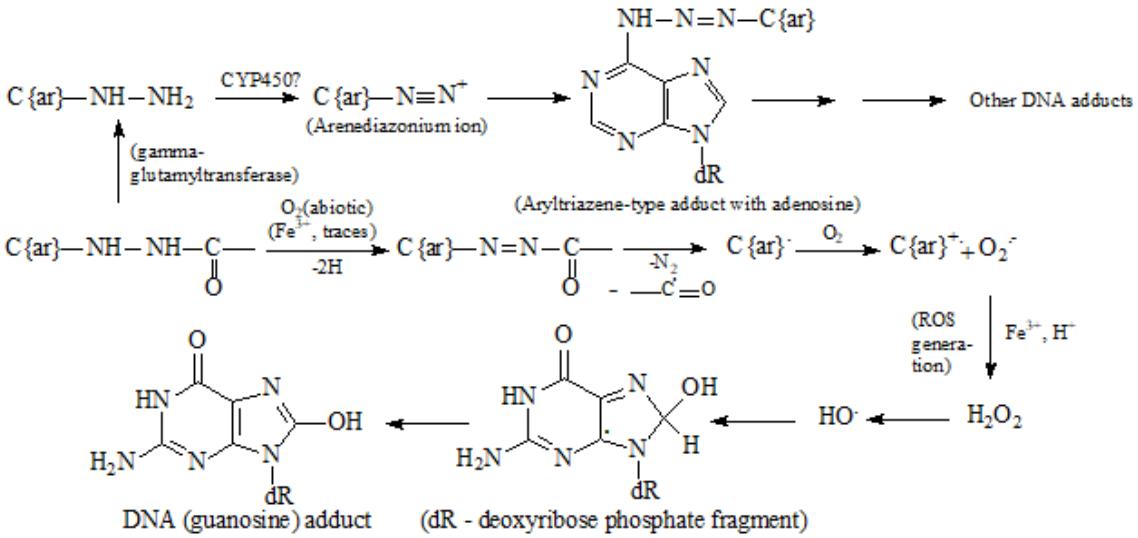
(Deoxycytidine)
(dR - deoxyribose phosphate fragment)
(Y can be alkyl, aryl or -H)

On the basis of the available literature data, the following generalized scheme is likely to operate *via* radical mechanism by ROS formation [5, 6, 7 - 9]:



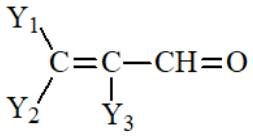
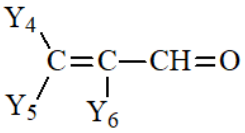
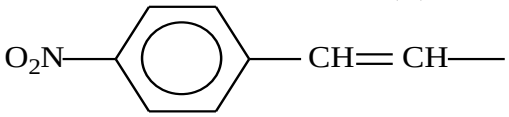
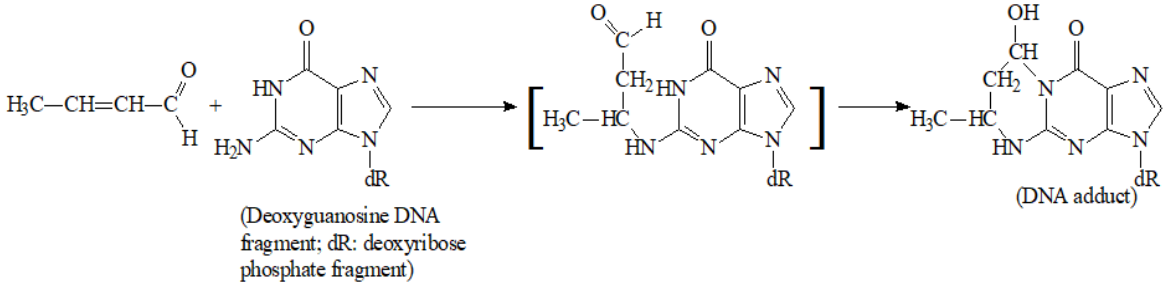
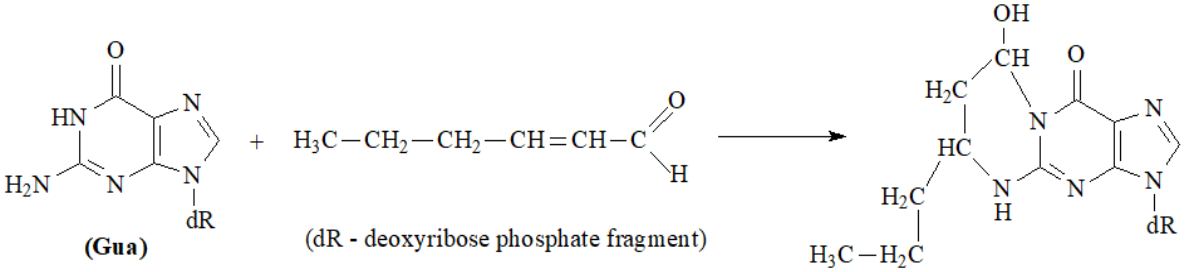
DNA (guanosine) adduct (dR - deoxyribose phosphate fragment)

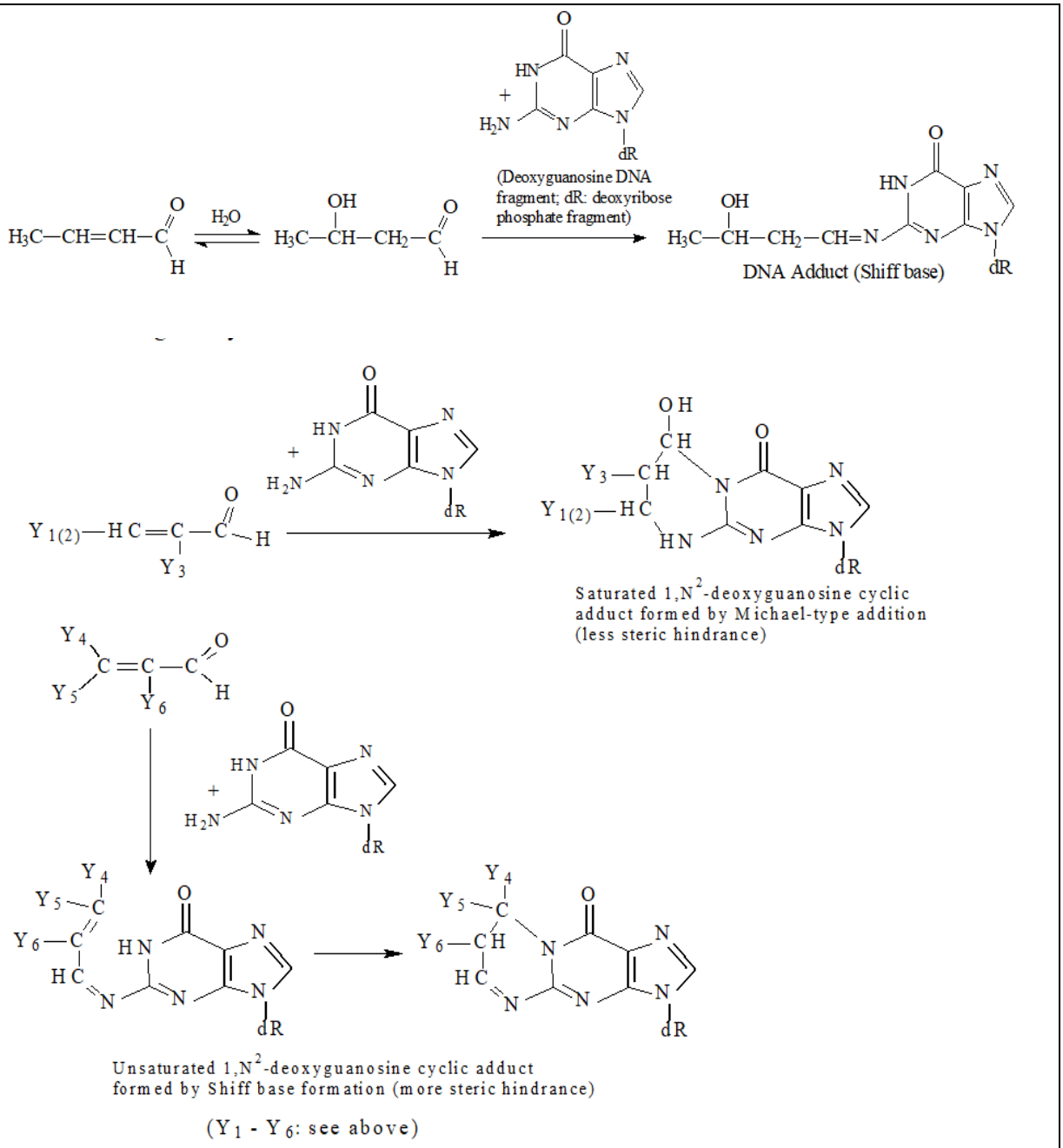
Based on the established abiotic oxidative consumption of agaritine and structurally similar chemicals, the following mechanistic scheme for the explanation of its mutagenicity can be expertly suggested:



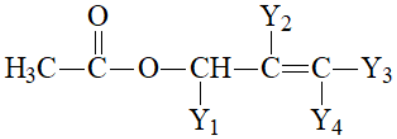
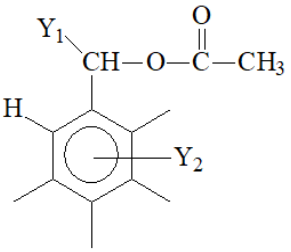
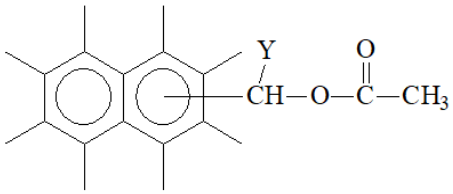
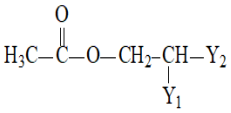
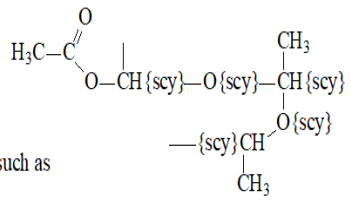
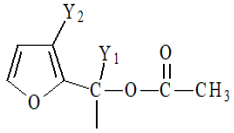
Set of chemicals used for profile development	Hydrazine Derivatives
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Phenylhydrazine, ICPS Inchem, Concise International Chemical Assessment Document 19; http://www.inchem.org/documents/cicads/cicads/cicad_19.htm#PartNumber:7 2. Parodi, S., Canc. Res. **41** (1981), 1469 – 1482. 3. Gilbert, W., *DNA Sequencing and Gene Structure*, Nobel Lecture, 8 December 1980; DOI: 10.1007/bf01116186. 4. Cashmore, A. R., Nucleic Acids Research **5**(7) (1978), 2485 – 2491. 5. Kalgutkar, A. S., Current Drug Metabol. **6** (2005), 161 – 225. 6. Kovacic, P., Current Med. Chem. **8** (2001), 773 – 796. 7. Rumyantseva, G., J. Biol. Chem. **266**(32) (1991), 21422 – 21427. 8. Quintero, B., Ars Pharmaceutica **41**(1) (2000), 27 – 46. 9. Gannet, P. M., Chem. Biol. Interact. **80**(1) (1991), 57 – 72. 10. *Chemical Carcinogenesis Research Information System (CCRIS)*; https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+ccris:@term+@rn+86-54-4 11. Friedrich, U., Z. Lebensm. Unters Forsch **183** (1986), 85 – 89. 12. Walton, K., Carcinog. **18**(8) (1997), 1603 – 1608. 13. Hajslova, H., Food Additives and Contaminants, 19(11) (2002), 1028 – 1033. 14. Sinha, B. K., J. Drug Metabol. & Toxicol. **5**(2) (2014), 1 – 6.

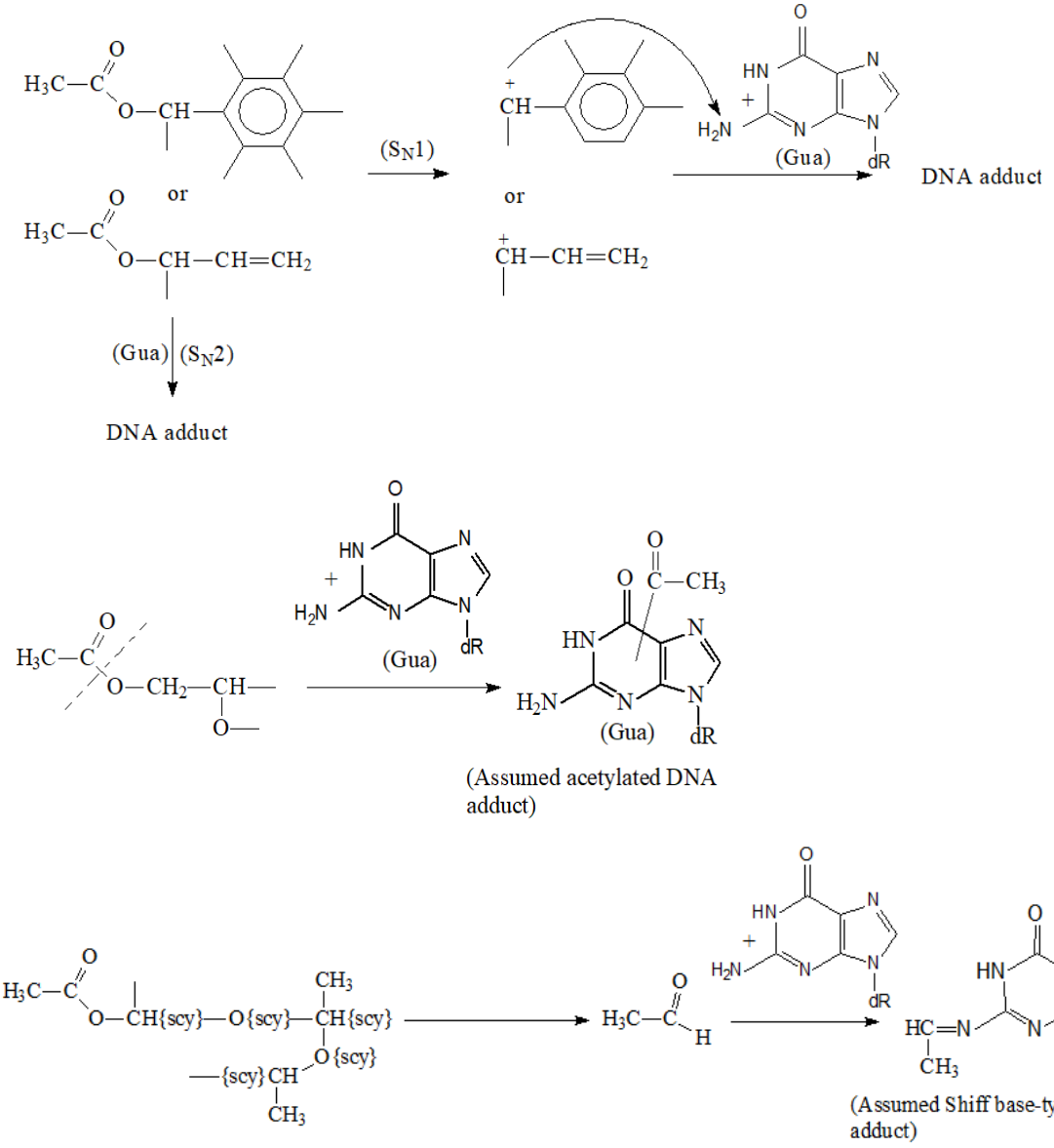
Individual profile/alert

Name	Alpha,Beta-Unsaturated Aldehydes
Type of profile	Structural alert
Description/applicability domain	 Y_1, Y_2 are H (both); or CH_3 (both); or combination of H and n-C_nH_{2n+1} (n = 1 – 4); or combination of H and H_3C-CH=CH- ; Y_3 is H *(Notes: 1. If both Y_1 and Y_2 are H, Y_3 can be also n-C_nH_{2n+1} (n = 1 – 4));* *2. If only one of Y_1 or Y_2 is H, Y_3 can be –CH_3)*  Y_4 and Y_5 are X (where X is Cl or Br); or combinations of X with –COOH, -CH=O, -NO_2 or -CN; or combinations of H with X or with –COOH, -CH=O, -NO_2 or –CN or combinations of H with –CH_2-O-C(O)CH_3 or with  ; Y_6 is –H, X or CH_3
Mechanism	**A_N2 Nucleophilic addition to α,β-unsaturated carbonyl compounds & A_N2 Shiff base formation**
 (Deoxyguanosine DNA fragment; dR: deoxyribose phosphate fragment)  (Gua) (dR - deoxyribose phosphate fragment) **DNA adduct**	



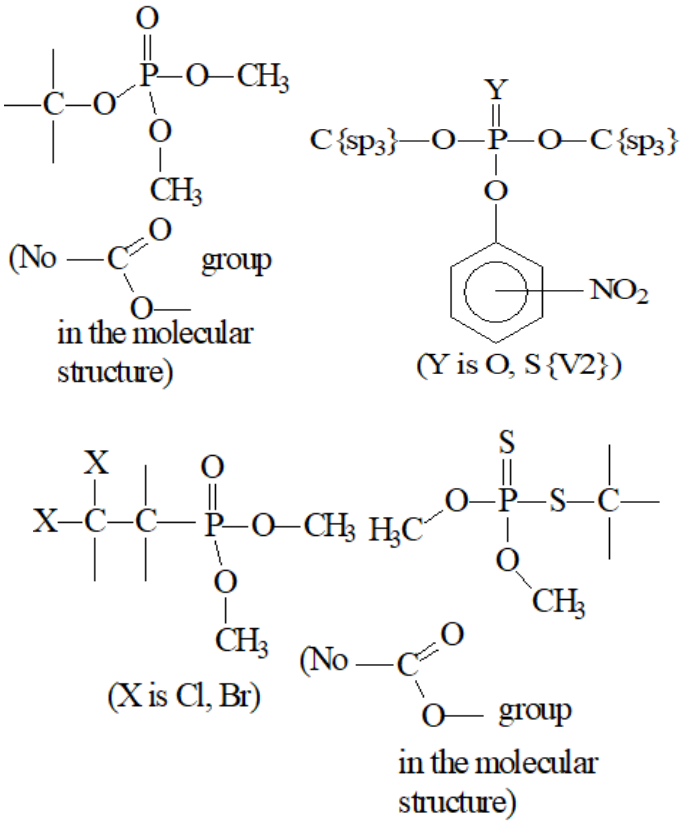
Set of chemicals used for profile development	Alpha,Beta-Unsaturated Aldehydes
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Eder, E., Environ. Health Persp. **88** (1990), 99 – 106. 2. Hecht, S. S., Toxicology **166** (1-2) (2001), 31 – 36. 3. Schuler, D., Carcinogenesis **20**(7) (1999), 1345 – 1350. 4. Hansen, E., Toxicol. Sci **81** (2004), 190 – 197. 5. Eder, E., Environ. Mol. Mutag. **37**(4) (2001), 324 – 328. 6. Lutz, D., Mutat. Res. **93** (1982), 305 – 315. 7. Wang, M., Chem. Res. Toxicol. **14** (2001), 423 – 430.

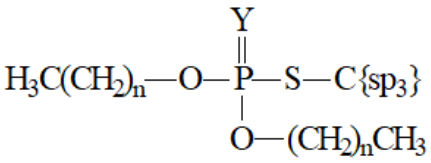
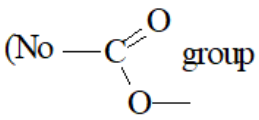
Individual profile/alert	
Name	Specific Acetate Esters
Type of profile	Structural alert
Description/applicability domain	 (Y_1: -H or C{ar}; Y_2, Y_3: -H or electron-withdrawing substituents such as -O-, -NO_2, -CN, -C(O)-, -CHO capable of conjugation); Y_4: -H or -C: number of C-atoms in Y_4 0 - 2)  (Single-ring, Y_1: -H or C=C; Y_2: electron-withdrawing substituents such as -O-, -NO_2, -CN, -C=O, -CHO, -OC=O); no more than three substituents)  (Fused-ring polycyclic derivative; Y can be -H or -CH_3)  (Y_1 and Y_2 can be OH and -CH_2OH or H and -O-CH_3 respectively; or -H and electron-withdrawing substituents such as -NO_2, -CN, -C=O, -CHO, -OC=O)   (Y_1 is -H or C{ar}; Y_2 is -H or EWG such as -O-, NO_2, -CN, -C=O, -CH=O, -OC=O)
Mechanism	**S_N1 Nucleophilic attack after carbenium ion formation, S_N2 Acylation, S_N2 at sp3 carbon atom & A_N2 Shiff base formation after aldehyde release**



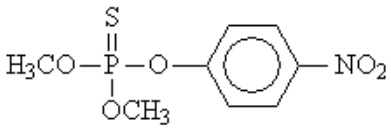
Set of chemicals used for profile development	Specific Acetate Esters
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Zeiger, E., Mutat. Res. **290** (1993), 53 – 61. 2. Rogan, E. G., Chem. Biol. Interact. **58** (1986), 253 – 273. 3. Auerbach, S. S., Toxicol. **253**(1 – 3) (2008), 79 – 88 4. Johanson, G., Crit. Rev. in Toxicol. **30**(3) (2000), 307 – 345 5. Tenant, R.W., Mutat. Res. **257** (1991), 209 – 227. 6. Glatt, H., Mutag. **27**(1) (2012), 41 – 48. 7. *NTP Technical Report on the Comparative Toxicity Studies of Allyl Acetate (CAS No. 591-87-7), Allyl Alcohol (CAS No. 107-18-6) and Acrolein (CAS No. 107-02-8) Administered by Gavage to F344/N rats and B6C3F1 Mice*, Tox. Rep. Ser. 48 (2006) 1 – 73, A1-H10 (Abstract); https://www.ncbi.nlm.nih.gov/pubmed/17160105, last visited 09.2019.

	8. *Acetin, Chemical Carcinogenesis Research Information System (CCRIS)*; https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+ccris:@term+@rn+26446-35-5

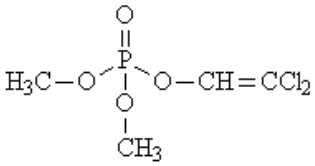
Individual profile/alert	
Name	Alkylphosphates, Alkylthiophosphates and Alkylphosphonates
Type of profile	Structural alert
Description/applicability domain	

	  in the molecular structure) (n = 0 - 1) (Y is O, S{V2})
Mechanism	**S_N2 Alkylation**

The compound methylparathion:



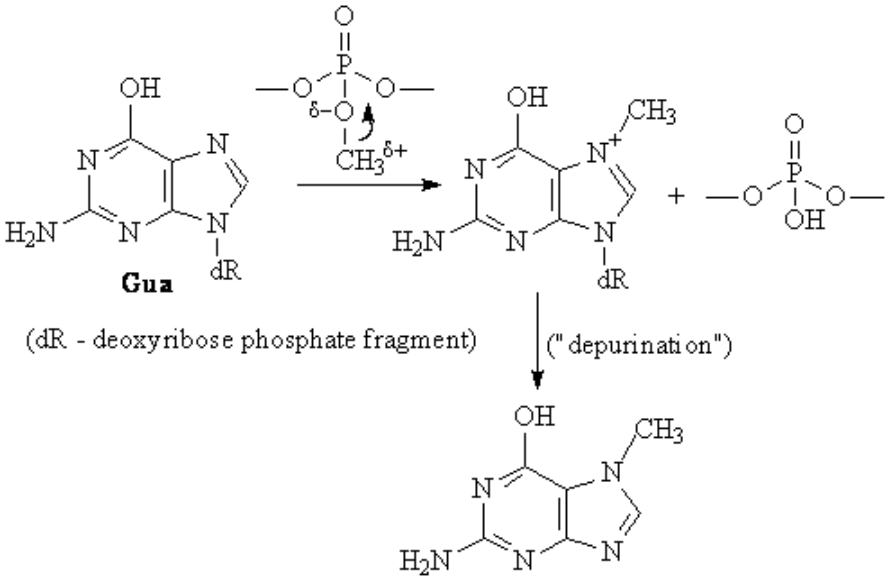
which belongs to the organothiophosphate group of insecticides also exhibits mutagenicity [2]: perhaps the aromatic nitro group strongly contributes to this effect. Alkylation of DNA has been proposed as the essential step for mutation interactions of the organophosphate insecticides dichlorovos and trichlorfon, and no evidence for a role of metabolic activation in the mutagenicity of these compounds was found [3]. Dichlorovos (O-(2,2-dichlorovinyl)-O,O-dimethylphosphate) (agricultural pesticide):



was found to be a relatively weak methylating agent, which was mutagenic as a parent as well as after metabolic activation. Dichlorvos was also shown to act as methylating agent of nucleophiles, and, more specifically, to induce strand breaks in isolated DNA [4, 5]. Moreover, dichlorvos (organic phosphate ester with dichlorovinyl side chain), and trichlorphon, which have similar structures were found to be mutagenic in the *Salmonella* strain TA1535 [6]. Also, the ability of other organophosphates and thiophosphates such as methylbromphenvinphos, methylparathion and malathion to elicit methylation of N7 of guanine fragment in DNA *in vitro* has been studied, and 7-methylguanine was the main methylation adduct [7]. This was confirmed by the findings that, generally, organophosphate insecticides, containing at least two methyl ester groups in their molecular structure such as *dichlorvos* and *naled* elicited *Ames* mutagenic activity [8].

Therefore, the alkylation mechanism seems to be more plausible for this class of

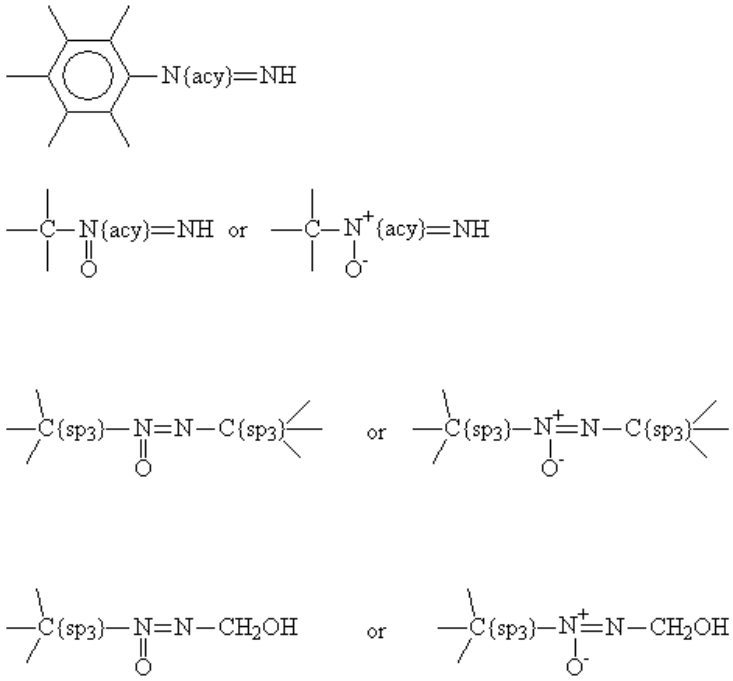
compounds, as expertly outlined below in Scheme 1



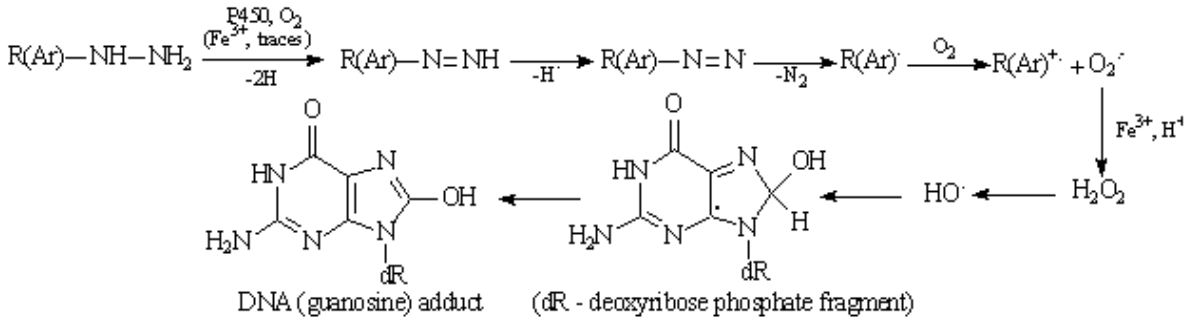
Scheme 1

Set of chemicals used for profile development	Alkylphosphates, Alkylthiophosphates and Alkylphosphonates
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. *Methyl Parathion*, IPCS Inchem, International Programme on Chemical Safety, Environmental Health Criteria 145; http://www.inchem.org/documents/ehc/ehc/ehc145.htm). 2. Wang, T. C., Zool. Studies **42**(3) (2003), 462 – 469. 3. Braun, R., Chem. Biol. Interact., **39**(3) (1982), 339 – 350. 4. *Mutagenicity of Dichlorovos*, Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment, January 2002; Ashwood-Smith, J. Trevino, R. Ring, Mutagenicity of Dichlorvos, Nature, 240 (1972), 418-420 5. Lofroth, G., Naturwissenschaften **57**(8) (1970), 393 – 394. 6. Carere, A., Chem.-Biol. Interact. **22** (1978), 297 – 308. 7. Wiaderkiewicz, Acta Biochim. Pol. **33**(2) (1986), 73 – 85; https://www.ncbi.nlm.nih.gov/pubmed/3766014 last visited 10.2019. 8. Hour, Mutagen. **13**(2) (1998), 157 – 166.

Individual profile/alert	
Name	Diazenes and Azoxyalkanes
Type of profile	Structural alert

Description/applicability domain	
Mechanism	**Radical ROS generation (indirect) and S_N1 Direct nucleophilic attack on diazonium cation (DNA alkylation)**

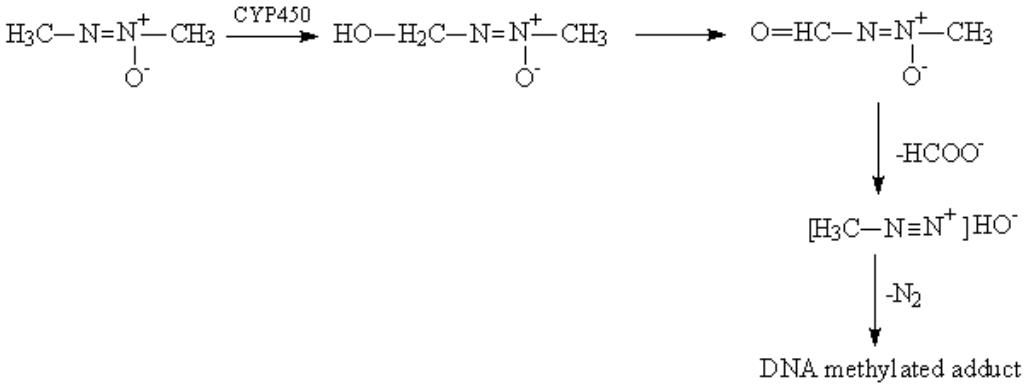
On the basis of the available literature data, the following generalized scheme, similar to those suggested for *Hydrazine Derivatives* and *Arenediazonium Salts* can be assumed to operate *via* radical mechanism by reactive oxygen species (ROS) formation [2 – 6] as shown in Scheme 1



Scheme 1

ROS can be also generated as a result from oxidation/reduction processes in bacteria without addition of exogenous S9 system. In such a case, the radical mechanism discussed above is likely to operate.

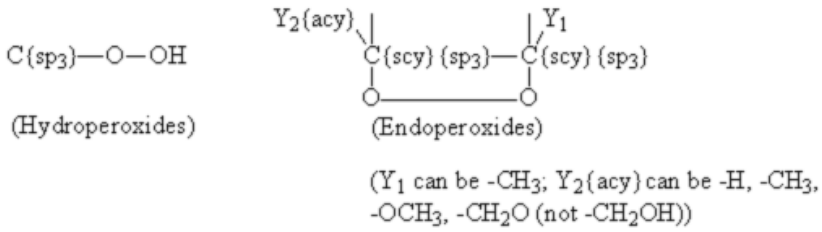
The metabolism of both the azoxymethane and methylazoxymethanol acetate is associated with an ester hydrolysis (for methylazoxymethanol acetate only), and microsomal oxidative N-dealkylation. The mutagenicity and DNA reactivity effects could be mainly due to generation of diazene and alkyl radicals or carbenium and alkanediazonium ions. The following mechanistic scheme of generation of reactive species has been suggested [9, 10] as shown in Scheme 2



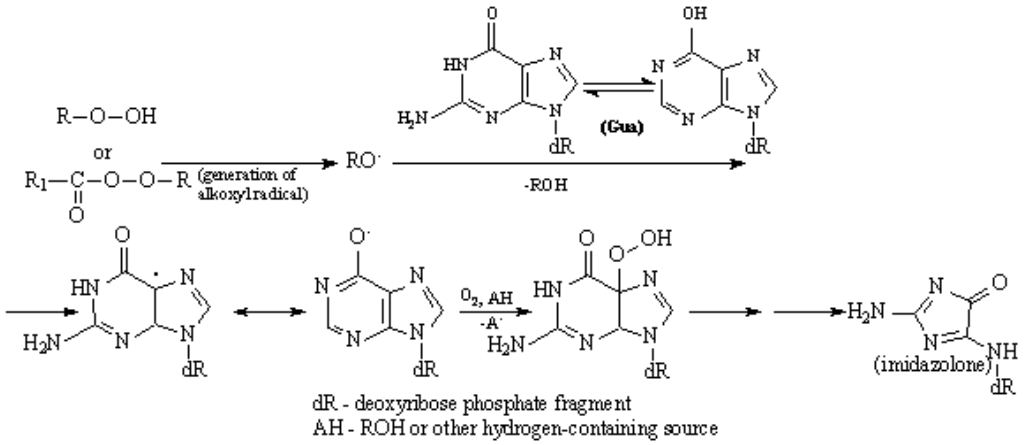
Scheme 2

Set of chemicals used for profile development	Diazenes and Azoxyalkanes
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Kosower, J. Am. Chem. Soc. **91**(9) (1969), 2325 – 2329. 2. Kalgutkar, Current Drug Metabol. **6** (2005), 161 – 225. 3. Kovacic, Current Med. Chem. **8** (2001), 773 – 796. 4. Rumyantseva, J. Biol. Chem. **266**(32) (1991), 21422 – 21427. 5. Quintero, Ars Pharmaceutica **41**(1) (2000), 27 – 46. 6. Gannet, Chem. Biol. Interact. **80**(1) (1991), 57 – 72. 7. CCRIS: *Methylazoxymethanol Acetate*, Toxicology Data Network, U.S. National Library of Medicine; http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+ccris:@term+@rn+592-62-1. 8. CCRIS: *Azoxymethane*, Toxicology Data Network, U.S. National Library of Medicine**;** http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+ccris:@term+@rn+25843-45-2). 9. Sohn, O. S., Carcinog. **12**(1) (1991), 127 – 131. 10. Campbell, Canc. Res. **38** (1978), 4585 – 4590. 11. Xiao, Mutagen. 11(3) (1996), 241 – 245.

Individual profile/alert	
Name	Organic Peroxy Compounds
Type of profile	Structural alert

Description/applicability domain	
Mechanism	**Radical ROS generation (indirect) or direct radical attack on DNA**

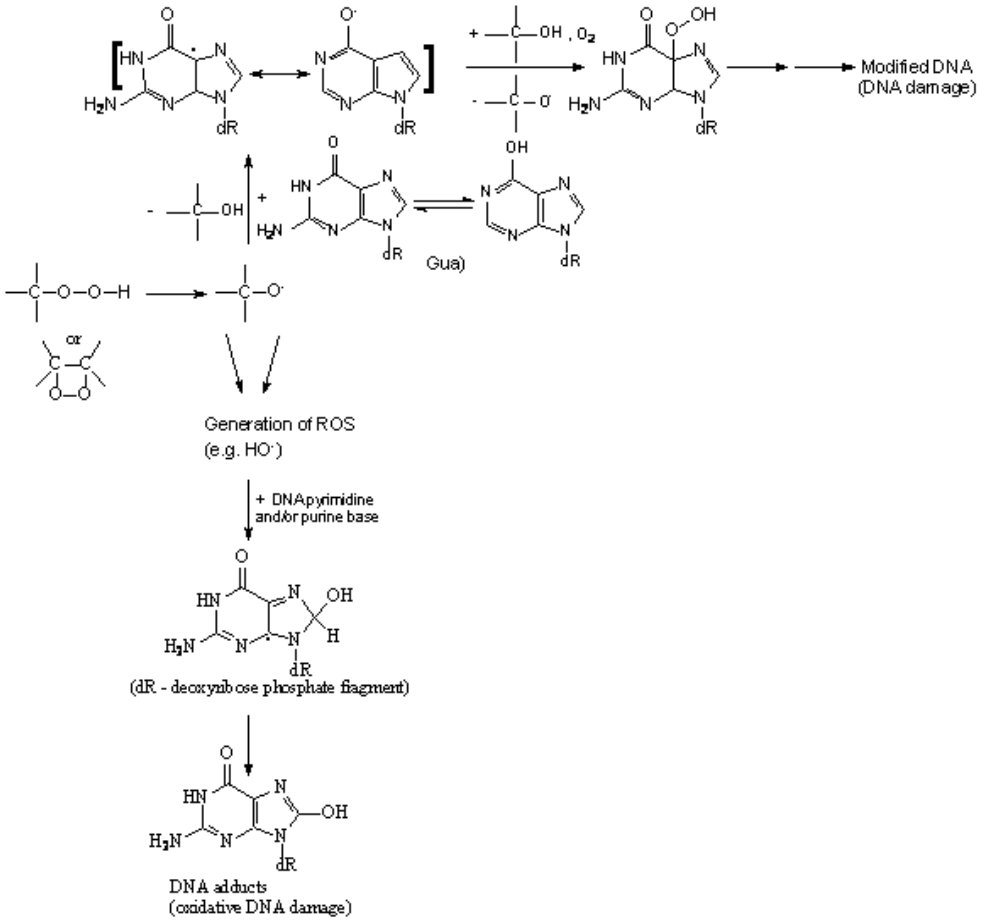
Alkoxyl radicals have been detected during the photolysis of water-soluble peroxyester, and, in the presence of DNA, oxidative damage of the latter was demonstrated *via* the formation of guanidine-releasing products by alkoxyl radicals, according to the following mechanistic scheme 1 [2]:



Scheme 1

Such radicals, similarly to the hydroxyl ones are also involved in the oxidative stress [2]. Mutagenicity of various organic peroxy compounds, including TBHP, cumene hydroperoxide, 1,2,3,4-tetrahydronaphtyhalene hydroperoxide, etc. has been observed.

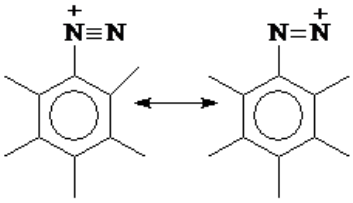
The following hypothetical mechanistic scheme for eliciting mutagenicity of hydroperoxides and endoperoxides can be assumed based on literature in Scheme 2 below.



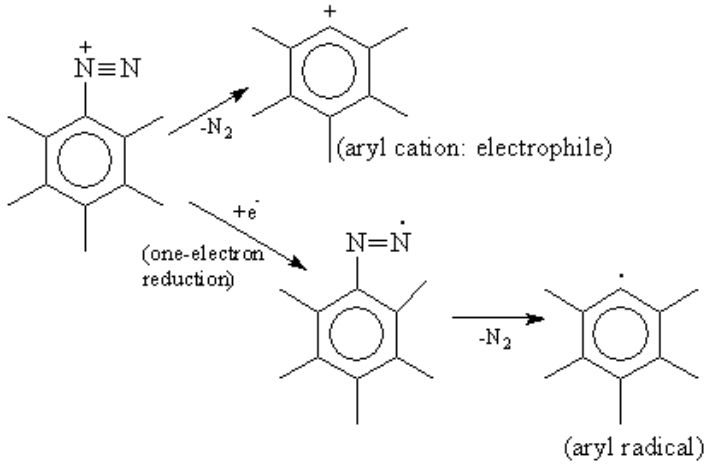
Scheme 2

Set of chemicals used for profile development	Organic Peroxy Compounds
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1.O· Donnel, Biochem. J. **304** (1994), 707 - 713. 2. Adam, Chem. Res. Toxicol. **11** (1998), 1089 - 1097. 3. Stock, S., Arch. Toxicol. **72**(6) (1998), 342 - 346. 4. Dillon, Mutagenesis **13**(1) (1998), 19 - 26. 5. Edenharder, Mutat. Res. **540**(1) (2003), 1 - 18. 6. Kovacic, Current Med. Chem. **8** (2001), 773 – 796. 7. Aust, Proc. Soc. Exp. Biol. Med. **222**(3) (1999), 246 – 252. 8. Valko, Chem. Biol. Interact. **160** (2006), 1 – 40. 9. Epe, Environ. Health Persp. **88** (1990), 111 – 115. 10. Hix, Chem.-Biol. Interact. **118** (1999), 141 – 149. 11. Mercer, J. Biol. Chem. **286**(2) (2011), 987 – 996.

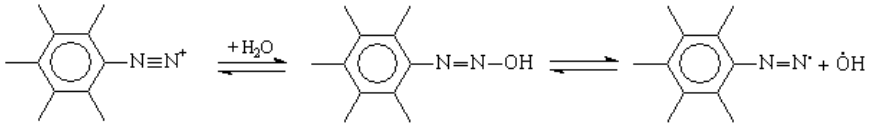
Individual profile/alert	
Name	Arenediazonium Salts
Type of profile	Structural alert

Description/applicability domain	
Mechanism	**S_N2 Direct nucleophilic attack on diazonium cation and Radical attack after one-electron reduction of diazonium cation**

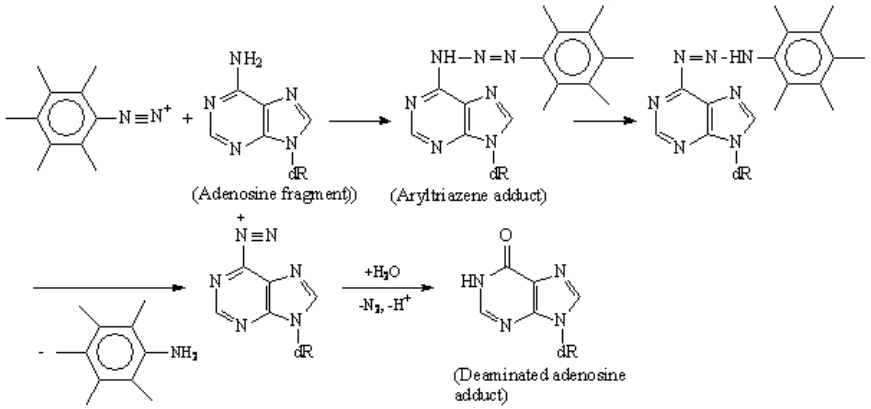
The decomposition pathways for arenediazonium ions can be expressed as follows:



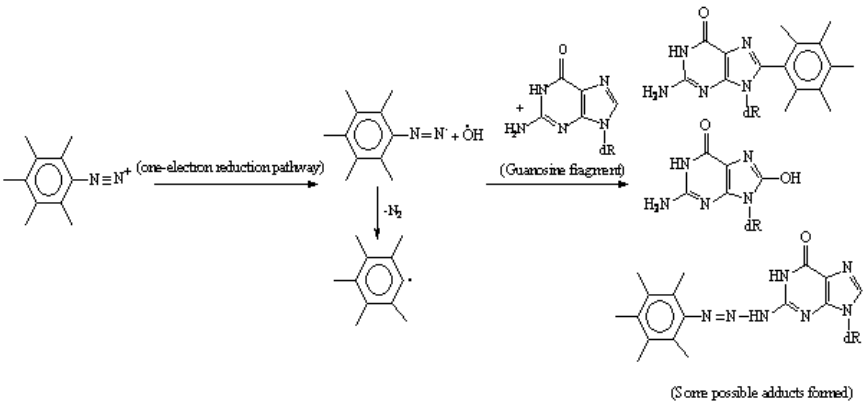
Also, hydroxyl radicals can be formed under these conditions:



When the arenediazonium ion is the reactive intermediate, the following scheme for the formation of adduct seems to be operative:

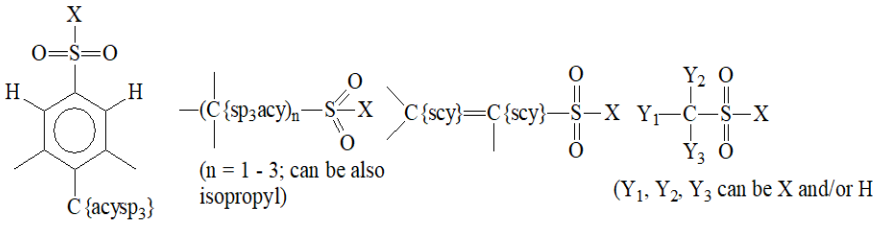
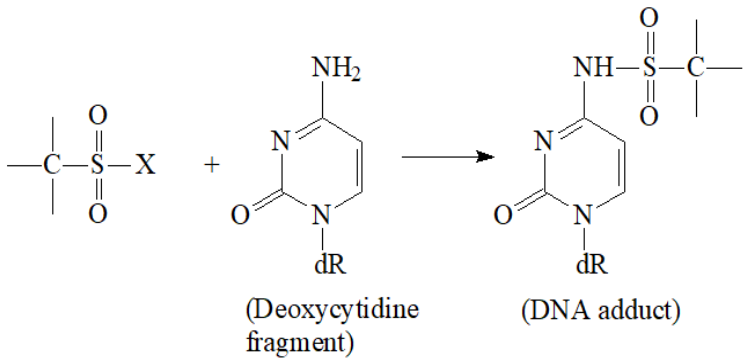


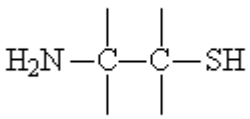
Alternatively, radical mechanism is also possible:

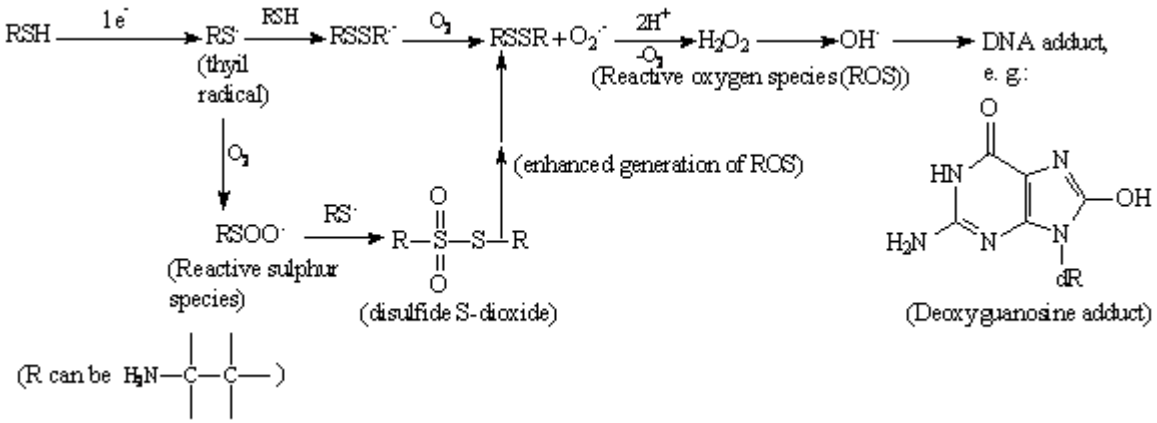


Set of chemicals used for profile development	Arenediazonium Salts
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Lawson, J. Agric. Food Chem. **43** (1995), 2627 – 2635. 2. Malaveille, Canc. Res. **42** (1982), 1446 – 1453.

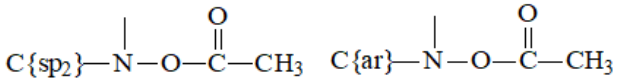
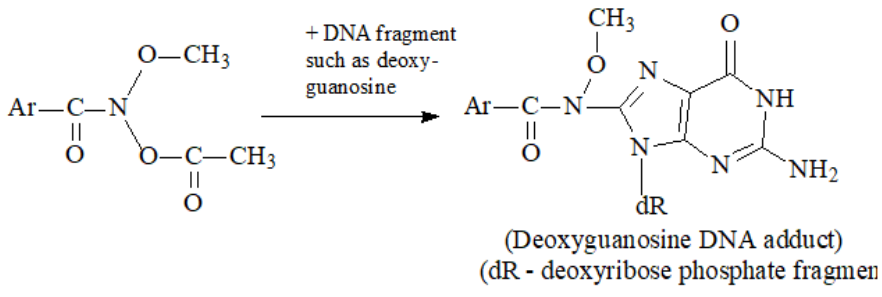
Individual profile/alert	
Name	Sulfonyl Halides
Type of profile	Structural alert

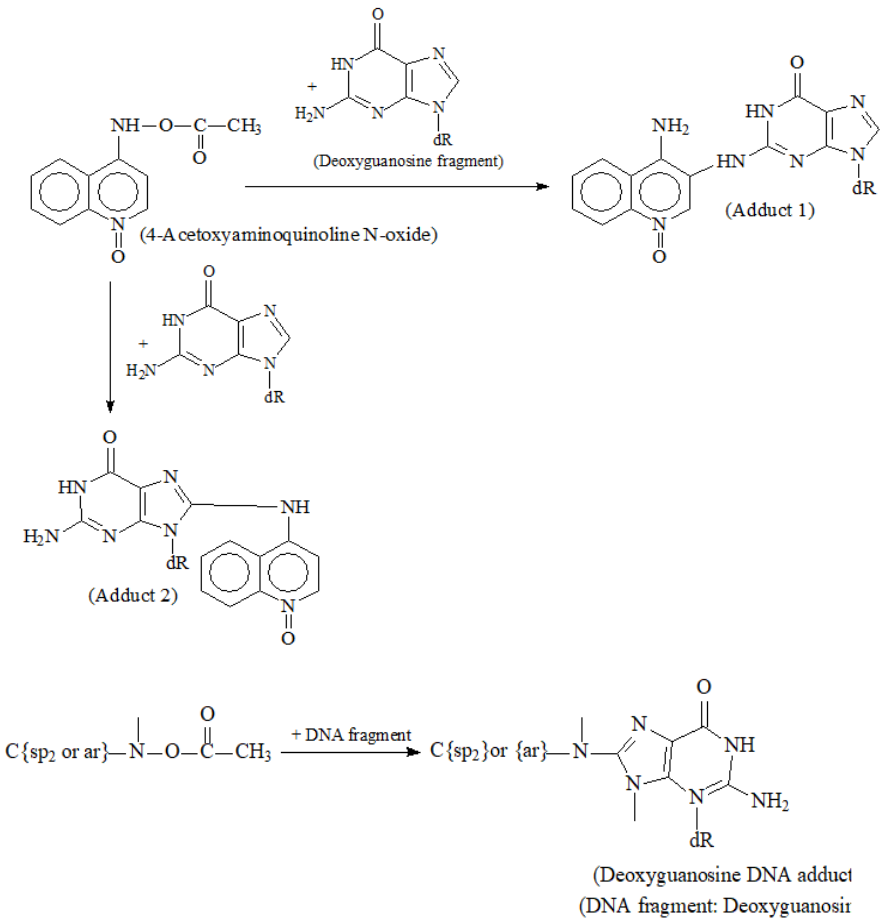
Description/applicability domain	
Mechanism	**S_N2 attack on sulfur atom**
	
Set of chemicals used for profile development	Sulfonyl Halides
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Sawatari, K., Ind. Health **39** (2001), 341 – 345. 2. Supek, Fr., Invest New Drugs **26** (2008), 97 – 110). 3. *4-Methylbenzenesulfonyl Chloride CAS No. 98-59-9*, SIDS Final Assessment Report for SIAM 17, Arona, Italy, 11 – 14 November 2003, OECD SIDS; http://www.eeaa.gov.eg/cmuic/cmuic_pdfs/generalpub/4-Methylbenzenesulfonyl%20chloride.pdf, last visited 10.2019. 4. Tsuchiya, Y., Water Sci & Technol. **25**(2) (1992), 123 – 130 (Abstract); https://iwaponline.com/wst/article/25/2/123-130/24352, last visited 10.2019.

Individual profile/alert	
Name	Thiols
Type of profile	Structural alert
Description/applicability domain	
Mechanism	**Radical ROS generation (indirect)**

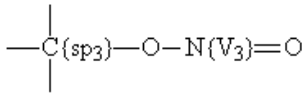


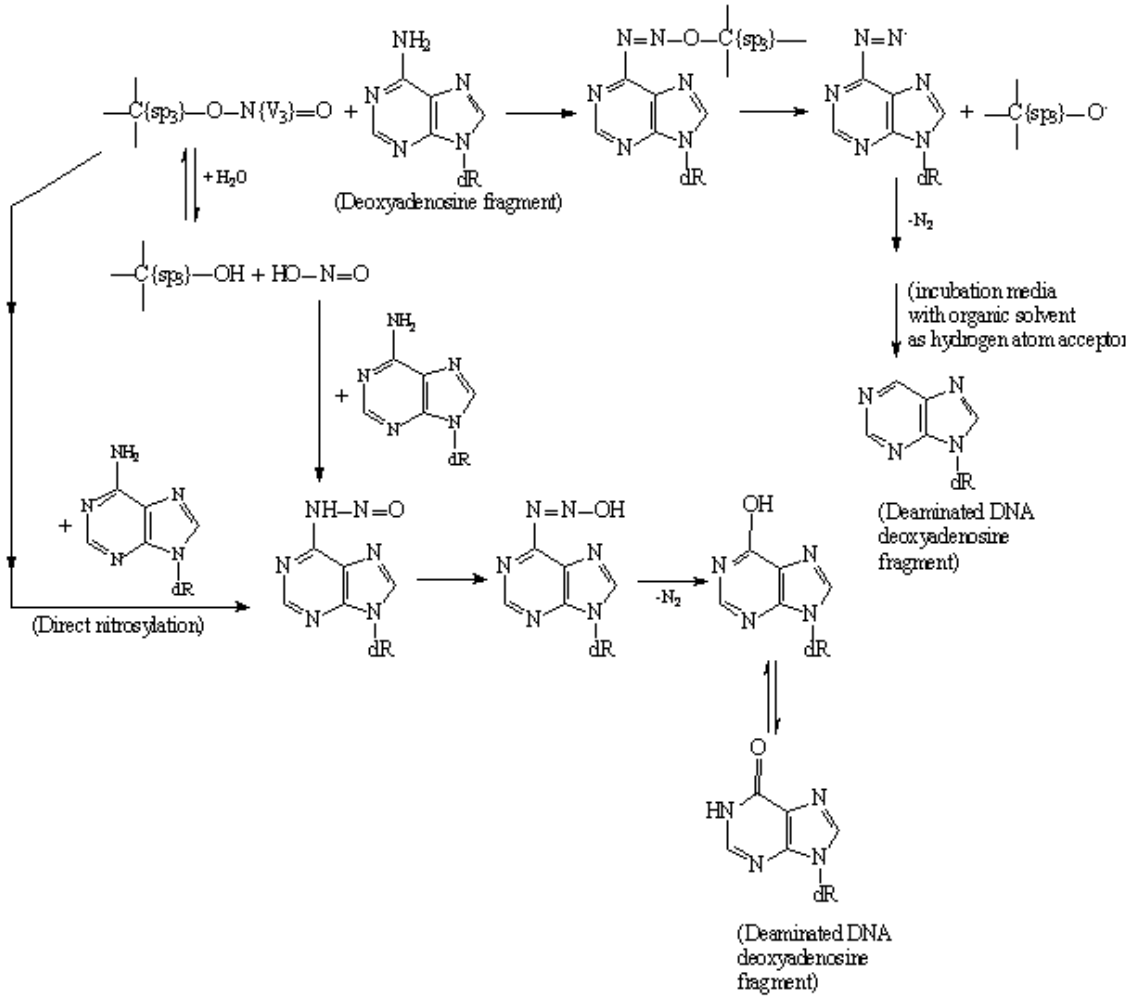
Set of chemicals used for profile development	Thiols
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Stark, A. A., Carcinog. 9(5) (1988), 771 – 777. 2. Sen, Ch. K., Am. J. Clin. Nutr. **72** (2000, 653S - 669S. 3. Jacob, C., Biochem. Soc. Transact **32** (2004), 1015 – 1017; http://www.biochemsoctrans.org/bst/032/bst0321015.htm. 4. Giles, G. I., Free Radic. Biol. Med. **31**(10), (2001), 1279 – 1983. 5. Kiley, P. J., PloS Biol. **2**(11) (2004), e400; https://doi.org/10.1371/journal.pbio.0020400, last visited 10.2019.. 6. Giles, G. I., Biochem. J. 364 (2002), 579 – 585.

Individual profile/alert	
Name	N-Acetoxyamines
Type of profile	Structural alert
Description/applicability domain	
Mechanism	**S_N2 reaction on a nitrogen-atom bound to a good leaving group**
	



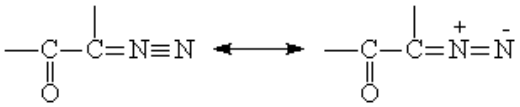
Set of chemicals used for profile development	N-Acetoxyamines
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Glatt, H., Carcinogenesis **25**(5) (2004), 779 – 786. 2. Banks, T. M., Org. Biomolec. Chem. **1**(13) (2003), 2238 – 2246. 3. Zoultina, S. G., Canc. Res. **45** (1985), 520 – 525.

Individual profile/alert	
Name	Alkylnitrites
Type of profile	Structural alert
Description/applicability domain	
Mechanism	**S_N1 or S_N2 Nitrosation, A_N2 Formation of adducts similar to Shiff bases and Radical DNA base deamination after radical decomposition**
The following generalized scheme for the formation of mutagenic species by alkylnitrites can be suggested based on literature	

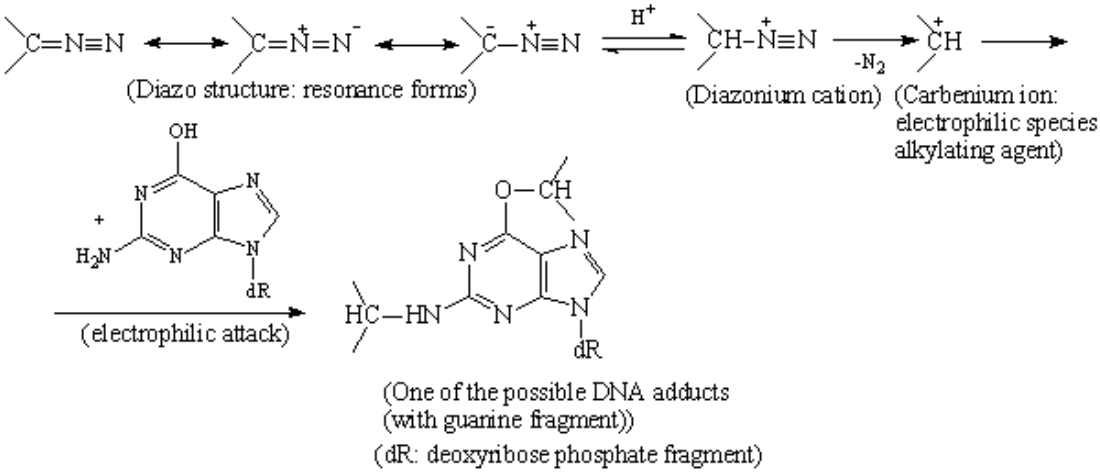


Set of chemicals used for profile development	Alkylnitrites
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Tornqvist, Mutat. Res. **117** (1983), 47 – 54. 2. Dunkel, Environ. Molec. Mutag. **14** (1989), 115 – 122). 3. *Organic Functional Group Transformations, Vol. 1 Synthesis: Carbon with No Attached Heteroatoms* (Ed. By A. R. Katritzky, O. M. Cohn, Ch. W. Rees, Elsevier Science Ltd. 1995; ISBN-13: 978-0080423227, ISBN-10: 0080423221. 4. Wild, Fd. Chem. Toxicol. **21**(6) (1983), 707 – 719. 5. Ehrenberg, Hereditas 92(1) (1980), 127 – 130).

Individual profile/alert	
Name	Diazoalkanes
Type of profile	Structural alert

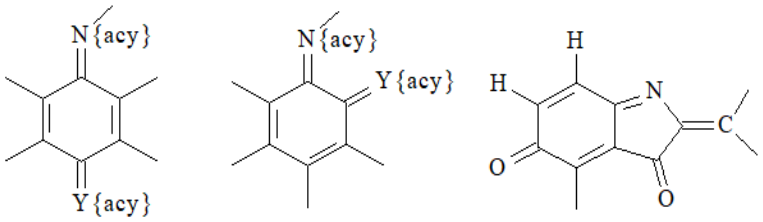
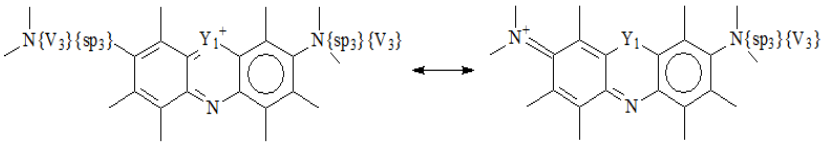
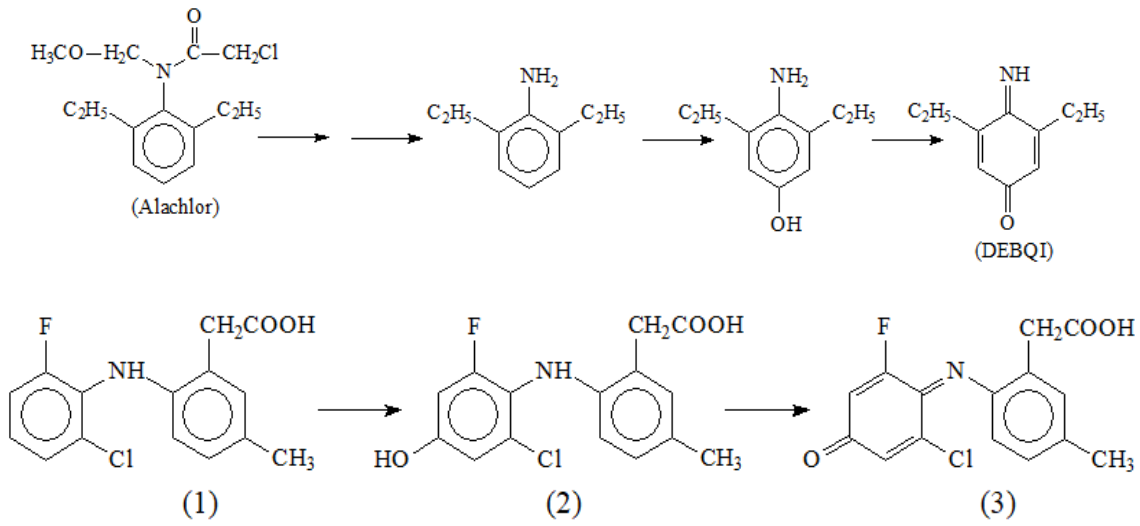
Description/applicability domain	
Mechanism	**S_N1 Alkylation by carbenium ion formed**

The following mechanistic scheme for DNA alkylation by this class of compounds can be assumed based on literature:

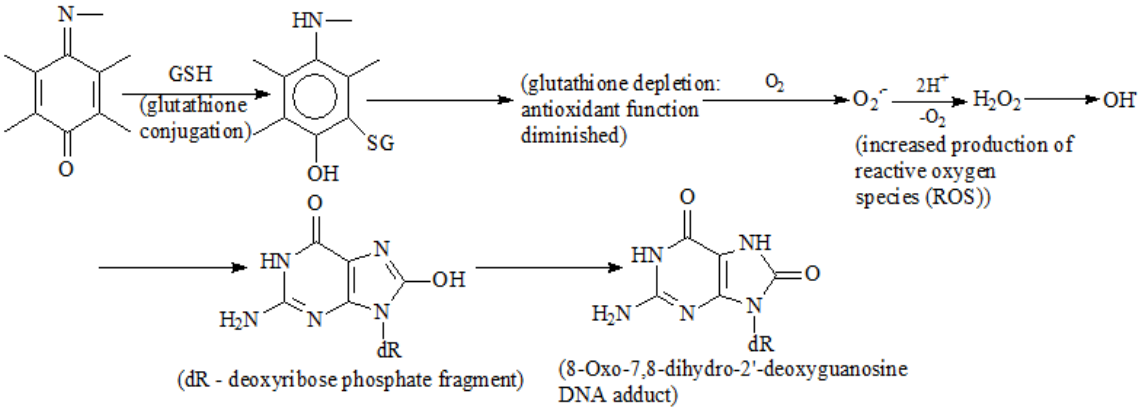


Set of chemicals used for profile development	Diazoalkanes
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1.L. Fishbein, Studies in Environmental Science, Vol. 4, Elsevier 1979, p. 118 - 134); http://www.sciencedirect.com/science/article/pii/S0166111608713177. https://doi.org/10.1016/S0166-1116(08)71317-7 Last visited 10.2019. 2. Pezacki, J. P., *Rate Constants and Mechanisms for Reactions of Carbenes and Cations from Oxadiazolines and Other Precursors*, Thesis for PhD degree, 1998, McMaster University. http://www.collectionscanada.gc.ca/obj/s4/f2/dsk1/tape7/PQDD_0028/NQ51008.pdf. Last visited 10.2019.. 3. Kusmierek, Nucl. Acids Res. **3**(4) (1976), 989 – 1000. 4. Farmer, Biochem. J. **135** (1973), 203 – 213.

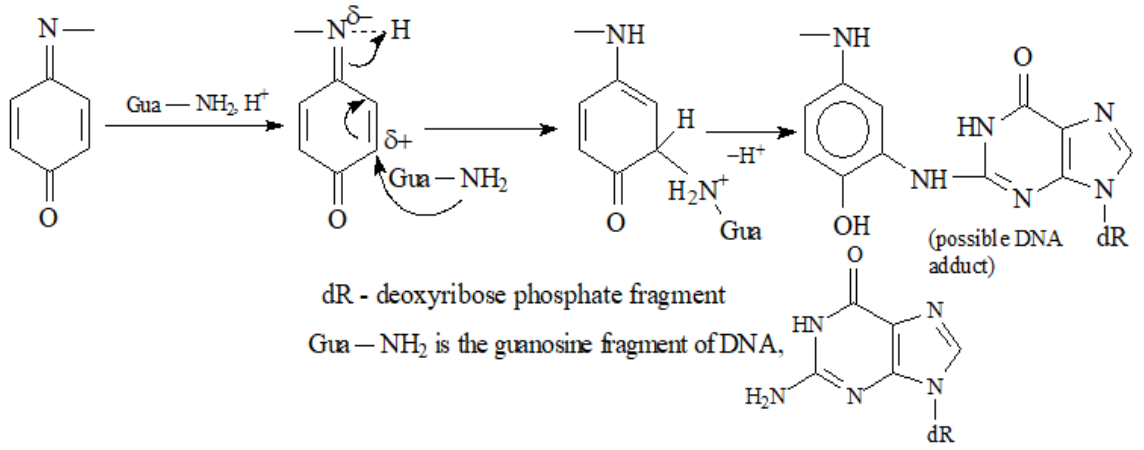
Individual profile/alert	
Name	Quinoneimine, Thione and Phenoxazinium Derivatives
Type of profile	Structural alert

Description/applicability domain	 (Y is O or N{V3}); {acy}: acyclic atom (No more than one *additional* substituent on the six-membered ring; (in case of $–CH_3$ and/or $–C_2H_5$ the number of *additional* substituents should be no more than two); No halogens (F, Cl, Br, I) or –OC{sp3} substituent(s) attached; General "mask": $-SO_3H$)  (Thionine and phenoxazinium derivatives) (Y_1 is S or O) (No more than one *additional* substituent attached; General "mask": $-SO_3H$)
Mechanism	**Radical ROS formation after GSH depletion (indirect), A_N2 Michael-type addition, quinoid structures & Non-covalent interactions DNA intercalation**
 I. **<u>Generation of reactive oxygen species (ROS)</u>.** It may be caused by an interaction with protein (enzyme) thiols or glutathione in the microsomal metabolic activation system. This mechanistic scheme seems to be plausible, since it is based on the interaction of "soft" nucleophile with "soft"	

electrophile as an *initial* molecular event, followed by generation of DNA-damaging ROS:



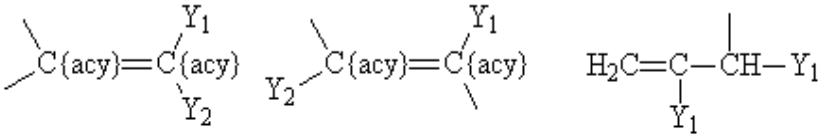
II. **Michael-type addition mechanism.** Such a scheme is regarded as less plausible, since it is based on the direct interaction of "soft" electrophile (quinoneimine derivative) with "hard" nucleophile (DNA base):

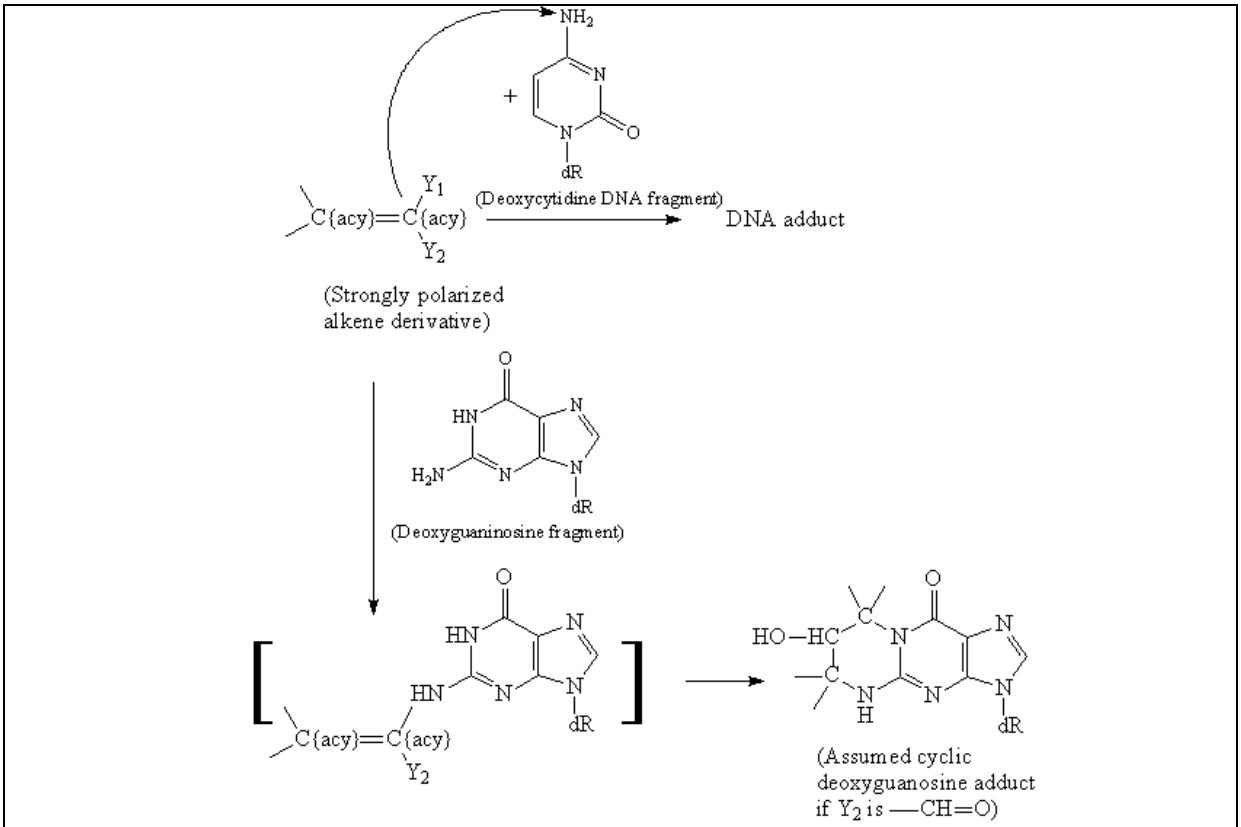


III. **DNA intercalation between DNA base pairs:** This mode of action could be associated with non-covalent interactions, due to the polycyclic planar structure of thionine and phenoxazinium derivatives, and their positively-charged resonance structures.

Set of chemicals used for profile development	Quinoneimine, Thionine and Phenoxazinium Derivatives
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Skipper, P. L., Carcinog. **31**(1) (2010), 50 – 58. 2. Rogers, L. K., Chem. Res. Toxicol. **10**(4), 1997, 470 – 476. 3. Cabbot, A. M., Chem. Res. Toxicol. **18**(11) (2005), 1721 – 1728. 4. Hill, A. B., Mutat. Res. **395** (1997), 159 – 171. 5. Stiborova, M., Mutat. Res. **500** (1 - 2) (2002), 49 – 66. 6. Bernadou, J., Proc. Natl. Acad. Sci. USA **81** (1984), 1297 – 1301. 7. Lemke, T. L., Lippincott Williams & Wilkins, 2002; http://www.amazon.com/Foyes-Principles-Medicinal-Chemistry Williams/dp/0683307371#reader_0683307371

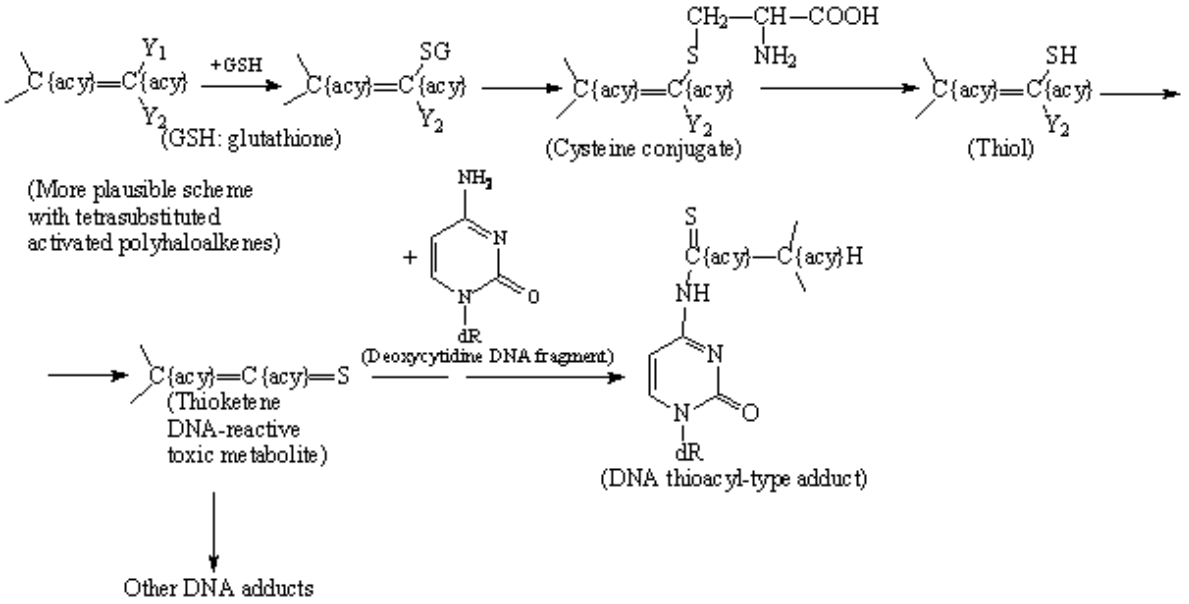
	8. Thompson, D. C., Mutat. Res. **279** (1992), 83 – 39. 9. Ying Li, Drug Metab. Dispos. **36** (2008), 469 – 473. 10. *Joicela, Lumiracoxib, Assessment Report EMA/CHMP/444155/2011*, Committee for Medicinal Products for Human Use (CHMP), European Medicines Agency; http://www.ema.europa.eu/docs/en_GB/document_library/Application_withdrawal_assessment_report/2011/11/WC500118339.pdf 11. Hesbert, A., Toxicol. Lett. **21**(1) (1984), 119 – 125 12. CCRIS: Indigo, Toxicology Data Network, U.S. National Library of Medicine; http://chem.sis.nlm.nih.gov/chemidplus/rn/482-89-3 13. Huang, M., Drug Metab. Dispos. **36** (2008), 2171 – 2184. 14. *1,4-Benzoquinone Dioxime*, IARC Monographs, Vol. 71, 1999; http://monographs.iarc.fr/ENG/Monographs/vol71/mono71-64.pdf 15. Westmoreland, C., Environ. Molec. Mutag. **19** (1992), 71 – 76. 16. Niufar, N. N., Rev. Soc. Quimica de Mexico **46**(4) (2002), 307 – 312. 17. Thionine, CCRIS, Toxicology Data Network, U.S. National Library of Medicine; https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+ccris:@term+@rn+581-64-6. 18. Methylene Blue, CCRIS, Toxicology Data Network, U.S. National Library of Medicine; https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+ccris:@term+@rn+61-73-4. 19. Basic Blue 3, Toxicology Data Network, U.S. National Library of Medicine; https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+ccris:@term+@rn+33203-82-6 20. Hossain, M., Mol. BioSyst **5** (2009), 1311 – 1322. 21. Hecht, Chr., *J. Phys. Chem. B* 108(29), (**2004)**, 10241 – 10244.

Individual profile/alert	
Name	Polarized Haloalkene Derivatives
Type of profile	Structural alert
Description/applicability domain	 (Y_1 is -Cl, -Br, -I; Y_2 is C(O) (carbonyl), -CN, -C-Cl, -C-Br, -C-I -OP(O)O- (phosphate group), -NO_2)
Mechanism	**S_N2 Alkylation, direct acting epoxides and related after P450-mediated metabolic activation, S_N2-type alkylation at sp3 and activated sp2 carbon atom, A_N2 Thioacylation *via* nucleophilic addition after thioketene formation and A_N2 Shiff base formation**
Direct alkylation (expertly assumed) – geminally bound halogen (Y_1) and strong electron-withdrawing substituent (Y_2) could make the former more labile, eliciting alkylating capability towards DNA pyrimidine and/or purine bases shown in Scheme 1:	



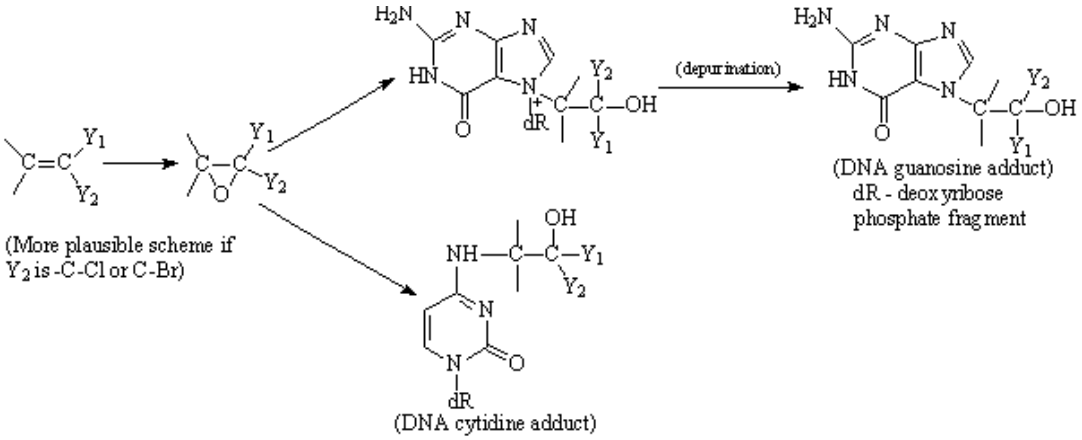
Scheme 1

Bearing in mind the structural similarity of compounds such as trichloropropenenitrile and 2-chloropentene-2-nitrile with other haloalkenes such as trichloroethylene, terachloroethylene, trichlorotrifluoropropene, etc., glutathione-dependent enzymatic metabolic bioactivation with the formation of active thioketene metabolite, catalyzed by phase II glutathione transferase and beta-lyase can be suggested for this class of chemicals [6, 7]. 3,N^4-Thioacetylcytosine has been, for example, identified as one of the DNA adducts with thioketene intermediates [8]. Therefore, by analogy, one of the possible mechanistic schemes that could be applied to this class of chemicals could be expertly suggested as follows shown in Scheme 2:



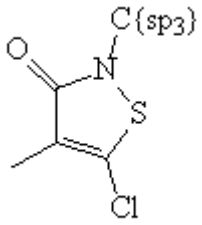
Scheme 2

Scheme III: Metabolic activation *via* epoxidation shown in Scheme 3:

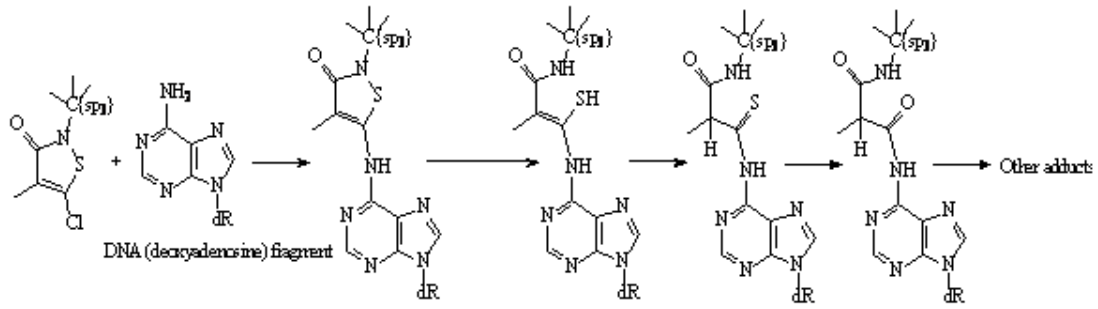


Scheme 3

Set of chemicals used for profile development	Polarized Haloalkene Derivatives
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Woo, Environ. Health Persp. **110** (Suppl. 1) (2002), 75 - 87. 2. Bull, Toxicol. **286** (2011), 1 – 19. 3. *Beta-Bromo-Beta-Nitrostyrene (CAS No. 7166-19-0) Administered by Gavage to F344/N rats and B6C3F1 Mice* (Prepared by J. R. Bucher), NTP, NIH Publication 94-3389, US Department of Health and Human Services, NIH, August 1994. 4. Eder, Mutat. Res. **322** (1994), 321 – 328. 5. Neudecker, Mutat. Res. **170** (1986), 1 – 9. 6. Kim, D., Drug Metab. Dispos. **34**, 2006, 2020 – 2027. 7. Decant, Environ. Health Persp. **88** (1990), 107 – 110. 8. Muller, Toxicol. **11**(5) (1998), 464 – 470;

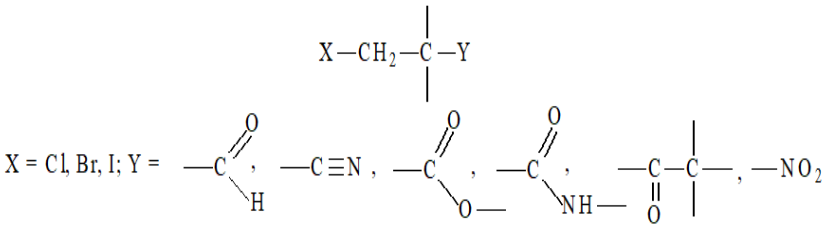
	http://pubs.acs.org/doi/abs/10.1021/tx9701440.
Individual profile/alert	
Name	Haloisothiazolinones
Type of profile	Structural alert
Description/applicability domain	
Mechanism	**Ring opening S_N2 reaction**

Despite the fact that no mechanistic schemes for DNA adduct formation with this class of chemicals have been found in the literature so far, it may be suggested that some potential DNA reactivity and adduct formation are possible. For example, the adenine base in DNA would perhaps react as nucleophile *via* its primary amino group with the haloizothiazolone chemical. This interaction is probably promoted by the thiol groups of CYP450 enzymes in the S9/microsomal fraction. It may happen, according to the following expertly assumed scheme, similar to that, proposed for the reaction with lysine primary amino group fragments in proteins [4]:

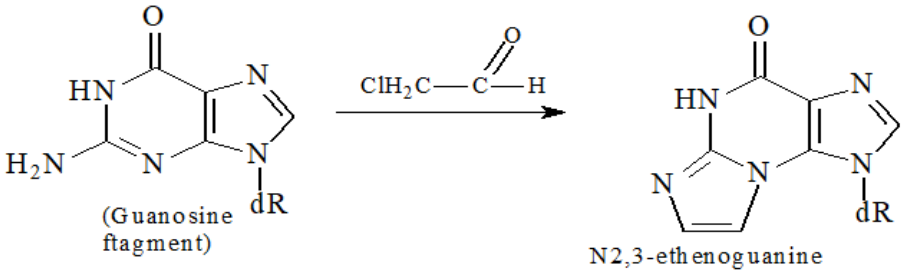


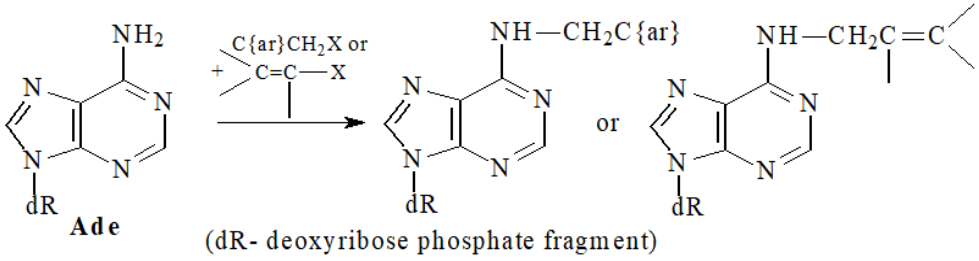
Set of chemicals used for profile development	Haloisothiazolinones
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1.Scribner, Mutat. Res./Gen. Toxicol. 118(3) (1983), 129 – 152. 2. Connor, Environ. Molec. Mutag. 28 (1996), 127 – 132. 3. Williams, PowerPlant Chemistry 9(1) (2007), 14 – 22. 4. Sanchez, Chem. Res. Toxicol. 17(9) (2004), 1280 – 1288.

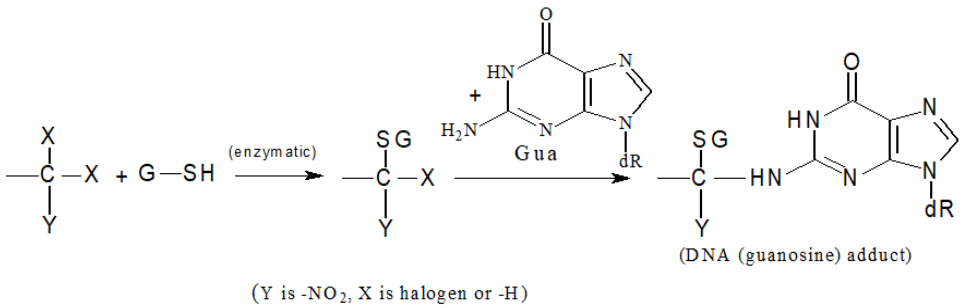
Individual profile/alert	
Name	Haloalkane Derivatives with Labile Halogen
Type of profile	Structural alert

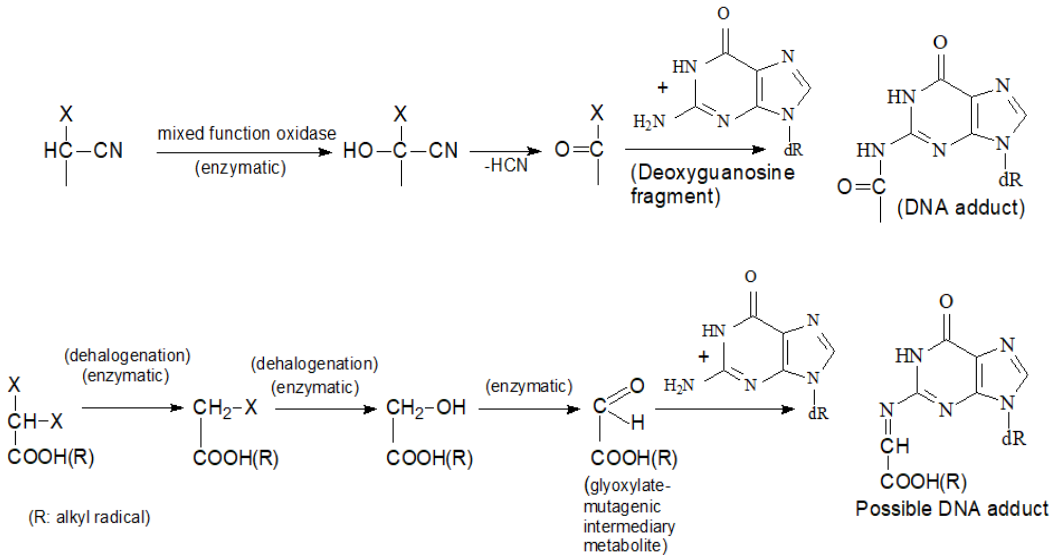
Description/applicability domain	$Y—CH_2X$ (Y can be C{ar}(no X attached to C{ar}, no more than two substituents attached on C{ar} (condensed rings not to be counted)); C=C; NO_2, C(O)O, C(O)H; X is Cl, Br, I) 
Mechanism	**S_N2 Alkylation, nucleophilic substitution at sp3-carbon atom, A_N2 Shiff base formation for aldehydes & S_N2 Acylation involving a leaving group**

1. Haloalkane derivatives with labile halogen at alpha-position towards other groups

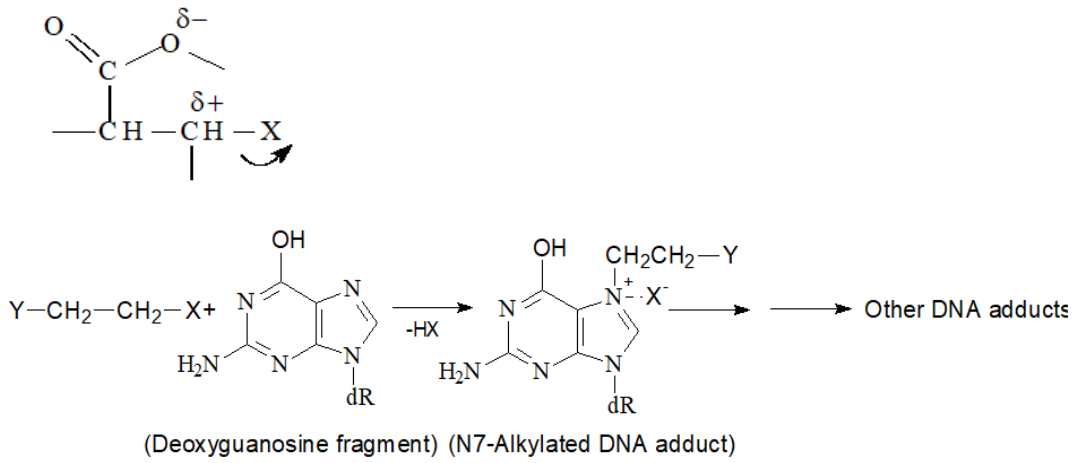






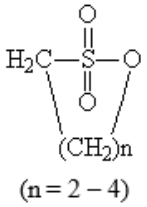


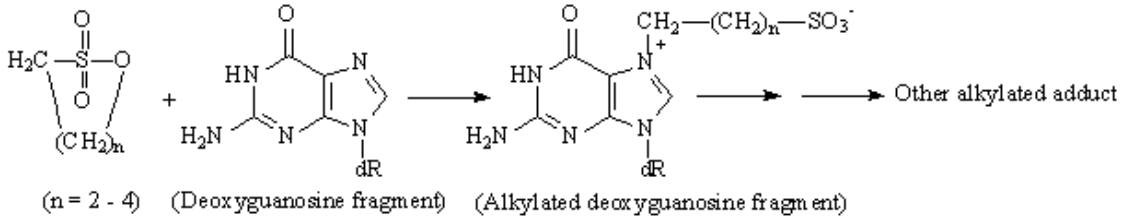
2. Haloalkane derivatives with labile halogen at beta-position towards other groups



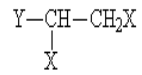
Set of chemicals used for profile development	Haloalkane Derivatives with Labile Halogen
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Woo, Y. T., Environ. Health Persp. **110** (2002), 75 – 87. 2. Kargalioglu, Y., Teratog. Carcinog. Mutag. **22**(2) (2002), 113-128; DOI: 10.1002/tcm.10010. 3. Plewa, M. J., Environ. Sci Technol. **38**(18), 2004, pp. 4713-4722; http://cfpub.epa.gov/si/si_public_record_report.cfm?dirEntryId=86035, last visited 09.2019. 4. Giller, S., Mutagenesis **12**(5) (1997), 321 - 328. 5. Oesch, Fr., Carcinogenesis **3** (6) (1982), 663 – 665; DOI: 10.1093/carcin/3.6.663. 6. Cheng, K. C., Proc. Natl. Acad. Sci USA **88** (1991), 9974 - 9978. 7. Fall, M., Mutat. Res. 633(1) (2007), 13 – 20; DOI: 10.1016/j.mrgentox.2007.04.017.

	8. Eder, E., Xenobiotica **12**(12), 1982, 831-848; DOI: 10.3109/00498258209038955. 9. Lin, E. L. C., Environ. Health Persp. **69** (1986), 67 – 71. 10. Kundu, B., Mutat. Res. **562**(1-2) (2004), 39 - 65. 11. Schneider, M., Mutat. Res. **439**(2) (1999), 233 - 238. 12. Brominated Acetic Acids in Drinking Water (Background Document for Development of WHO Guidelines for Drinking Water Quality, WHO/SDE/WSH/03.04/79 (2004); http://www.who.int/water_sanitation_health/dwq/chemicals/brominatedaceticacids.pdf 13. *Toxicological Review of Dichloroacetic Acid (CAS No. 79-43-6)*, In Support of Summary Information on the Integrated Risk Information Systme (IRIS), US EPA, Washington DC, August 2003; http://www.epa.gov/iris/toxreviews/0654tr.pdf. 14. *Monochloroacetic Acid in Drinking Water* (Background Document for Development of WHO Guidelines for Drinking Water Quality), WHO/SDE/WSH/03.04/85, WHO, 2004; http://www.who.int/water_sanitation_health/dwq/chemicals/monochloroaceticacid.pdf. 15. Theiss, J. C., Canc. Res. **39**, 1979, 391 - 395. 16. Colburn, N. H., Canc. Res. **28** (1968), 653 – 660. 17. Fall, M., Mutat. Res. 633(1) (2007), 13 – 20; DOI: 10.1016/j.mrgentox.2007.04.017. 18. *Allyl Bromide CAS No. 106-95-6, CSWG Evaluation* (12/16/94); http://ntp.niehs.nih.gov/ntp/htdocs/Chem_Background/ExSumPdf/AllylBromide.pdf 19. Eder, E., Xenobiotica 12(12), 1982, 831-848; DOI: 10.3109/00498258209038955. 20. McCoy, E. C., Mutat. Res./Fund. Molec. Mechan. Mutag. 57(1) (1978), 11 – 15; http://www.sciencedirect.com/science/article/pii/0027510778902294.

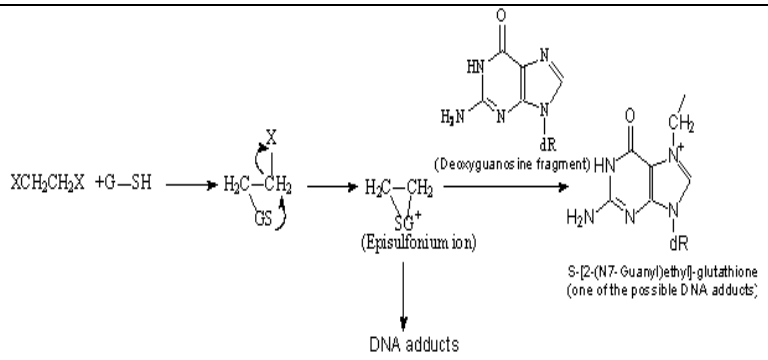
Individual profile/alert	
Name	Sultones
Type of profile	Structural alert
Description/applicability domain	 (n = 2 – 4)
Mechanism	**Ring opening S_N2 (alkylation)**
DNA-alkylating capability and the *in vitro* genotoxicity of sultones can be expertly suggested:	



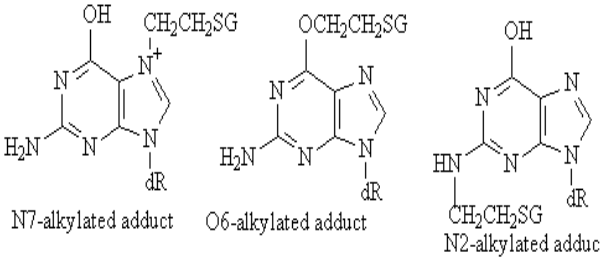
Set of chemicals used for profile development	Sultones
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. *1,3-Propane Sultone, Exposure Data*, IARC Monographs Vol. 71, 1095 – 1102; ISBN-13 (PDF): 978-92-832-1571-4. 2. *1,4-Butane Sultone* [MAK Value Documentation, 1992], The MAK Collection for Occupational Health and Safety; DOI: 10.1002/3527600418.mb163383isme0004. 3. Kubinski, J. Bacteriol. **136**(3) (1978), 854 – 866). 4. Golker, Chem.-Biol. Interact. **14** (1976), 195 – 202. 5. Hemminki, Carcinog. **4**(7) (1983), 901 – 904).

Individual profile/alert	
Name	Vicinal Dihaloakanes
Type of profile	Structural alert
Description/applicability domain	 (Y is –H, -$(CH_2)_nH$ (n = 1, 2), -$O(CH_2)_nH$ (n = 0 -2), -CH_2-O-, C{acy}{sp2}; No other halogens bound to Y)
Mechanism	**Internal S_N2 reaction with aziridinium and/or cyclic sulfonium ion formation and DNA alkylation**

1,2-dichloroethane is reasonably anticipated to be a human carcinogen, based on sufficient evidence of carcinogenicity in experimental animals. *In vivo* and *in vitro* studies in rodents have revealed that the primary metabolic pathway for 1,2-dichloroethane probably involves conjugation with glutathione, and the compound shows bacterial mutagenicity. This is S_N2 (bimolecular nucleophilic attack) of glutathione GSH on the electron-deficient carbon of 1,2-dichloroethane (also for 1,2-dibromoethane, 1,2-dichloropropane, etc.) and S-(2-chloroethyl)-glutathione adduct is formed. One of the further possible metabolic pathways is the loss of chloride ion with the formation of *episulfonium ion*, which is highly reactive. This ion is believed to be the reactive *electrophilic* intermediate that results in covalent reaction with biopolymers such as DNA, and is believed to determine the mutagenic potential of this class of organic halides [1 – 4, 6]:



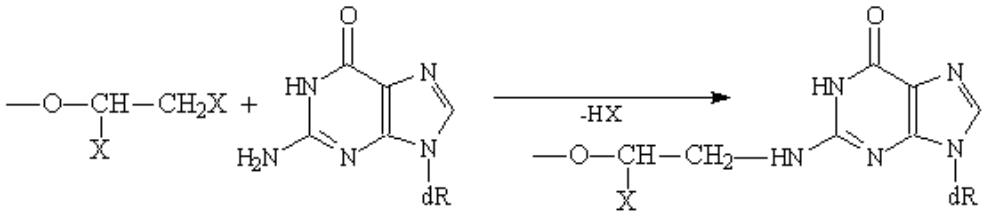
The major product of this reaction is *S*-[2-(*N*^{7}-guanyl)ethyl]glutathione, but *N*^{2}- and *O*^{6}-guanyl adducts are also formed, and all three adducts are potentially mutagenic [3]:



(dR - deoxyribose phosphate fragment)

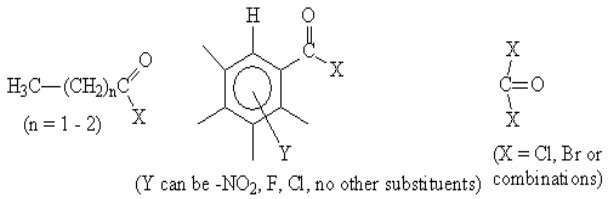
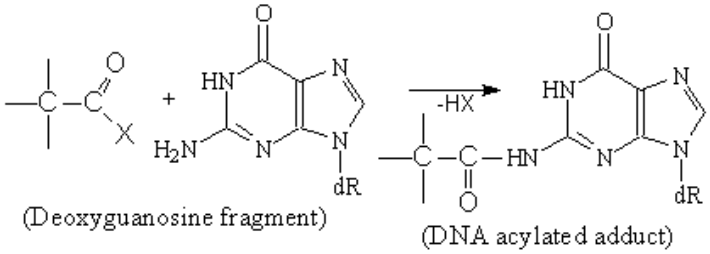
Similar mechanism of *in vitro* metabolic activation by forming episulfonium cation as reactive intermediate has also been suggested for structurally similar short-chain compounds such as 1,2-dibromo-3-chloropropane [5].

Beside 1,2-dichloroethane, 1,2-dibromoethane belonging to this class of compounds was also found to possess bacterial mutagenicity [7]. Short-chain vicinal dihalolakanes with halogen attached to terminal carbon atom are assumed to act by direct alkylation mechanism, too. Other short-chain vicinal haloalkane derivatives with electron-withdrawing heteroatoms adjacent to the –CHX fragment such as 1-methoxy-1,2-dichloroethane, 2,3-dibromo-propanol, etc., are believed to cause also direct mutagenicity by alkylation mechanism:



Set of chemicals used for profile development	Vicinal Dihaloalkanes
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Anders, Drug Metabol. Rev. **36** (3 – 4) (2004), 583 – 594. 2. *Public Health Goal for 1,2-Dichloropropane in Drinking Water*,

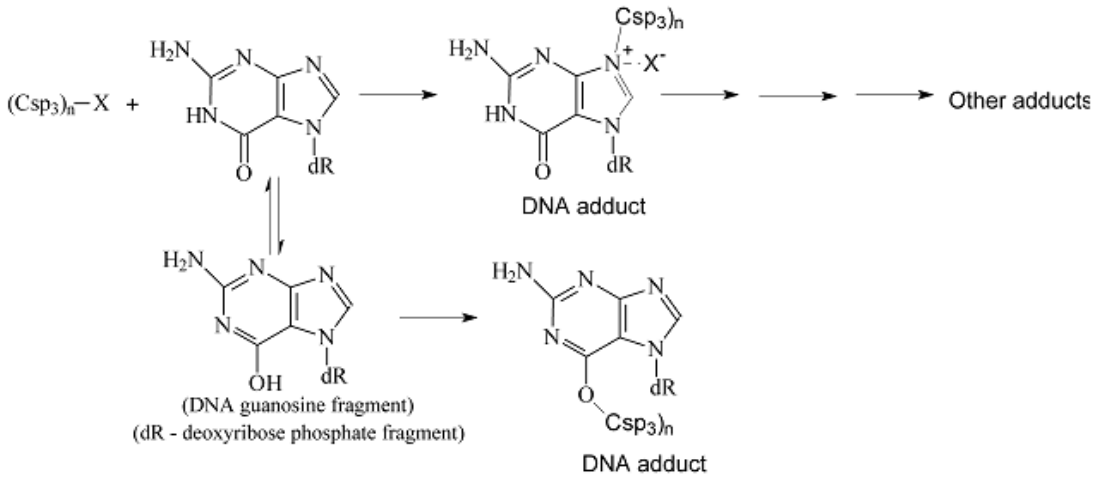
	Office of Environmental Health Hazard Assessment, California EPA, February 1999; http://www.oehha.ca.gov/water/phg/pdf/12dcp_f.pdf. 3. Guengerich, Environ. Health Persp. **76** (1987), 15 – 18. 4. Liu, J. Biol. Chem. **277** (40) (2002), 37920 - 37928. 5. 5. Miller, J. Toxicol. Environ. Health: Current Issues **19**(4) (1986), 503 – 518. 6. Rannug, Chem.-Biol. Interact. **20** (1978), 1 – 16. 7. Strubel, K., Toxicol. Environ. Chem. **15**(1-2) (1987), 101 – 128.

Individual profile/alert	
Name	Acyl Halides
Type of profile	Structural alert
Description/applicability domain	
Mechanism	**S_N2 Direct acylation involving a leaving group**
A mixture of methylglyoxal and hydrogen peroxide has been found to react with 2'-deoxyguanosine to form N^2-acetyl-2'deoxyguanosine [3]. By analogy, direct DNA acylation mechanism by acyl halides such as acetyl chloride can be expertly suggested: 	
Set of chemicals used for profile development	Acyl Halides
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. World Health Organization, International Agency for Research on Cancer, α-Chlorinated Toluenes and Benzoyl Chloride in Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, 1999, Vol. 71, pp 453-477. http://monographs.iarc.fr/ENG/Monographs/vol71/mono71-19.pdf. ISBN-13 (Print Book) 978-92-832-1271-3; ISBN-13 (PDF) 978-92-832-1571-4; 2. Sawatari, K., Nakanishi, Y., Matsushima, T., Relationships between chemical structures and mutagenicity: a preliminary survey for a database of mutagenicity test results of new work place chemicals. Ind. Health, 2001, 39(4), 341-345.

	3. Zeiger, E., Anderson, B., Haworth, S., Lawlor, T., Mortelmans, K., Speck, W., Salmonella mutagenicity tests: III. Results from the testing of 255 chemicals. Environ. Mutagen., 1987, 9(Suppl. 9), 1-109. 4. Tada, A., Wakabayashi, K., Totsuka, Y., Sugimura, T., Tsuji, K., Nukaya, H., 32P-Postlabeling analysis of a DNA adduct, an N2-acetyl derivative of guanine, formed in vitro by methylglyoxal and hydrogen peroxide in combination. Mutat. Res., 1996, 351(2), 173-180.

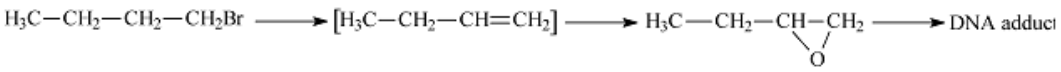
Individual profile/alert	
Name	Monohaloalkanes
Type of profile	Structural alert
Description/applicability domain	**$(C(sp^3)(acy))_n$-X(n=1-4; X=-Cl, -Br, -I)**
Mechanism	**S_N2 Alkylation, nucleophilic substitution at sp3-carbon atom, S_N1 Nucleophilic substitution after carbenium ion formation and S_N2 Alkylation by epoxide metabolically formed after E2 reaction**

Direct-Acting Mutagens – DNA alkylation in Scheme 1:

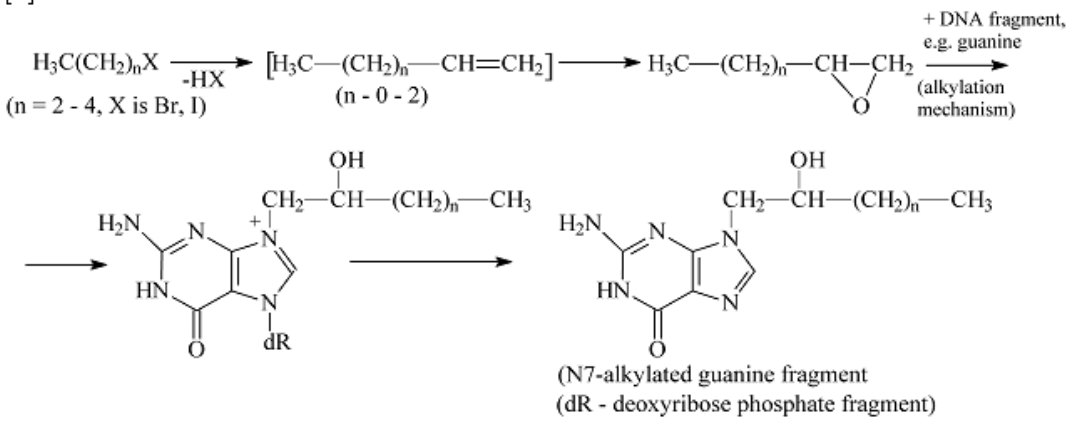


Scheme 1

Metabolic Activation (Bioactivation) (Exogenous S9 System Added) in Scheme 2:



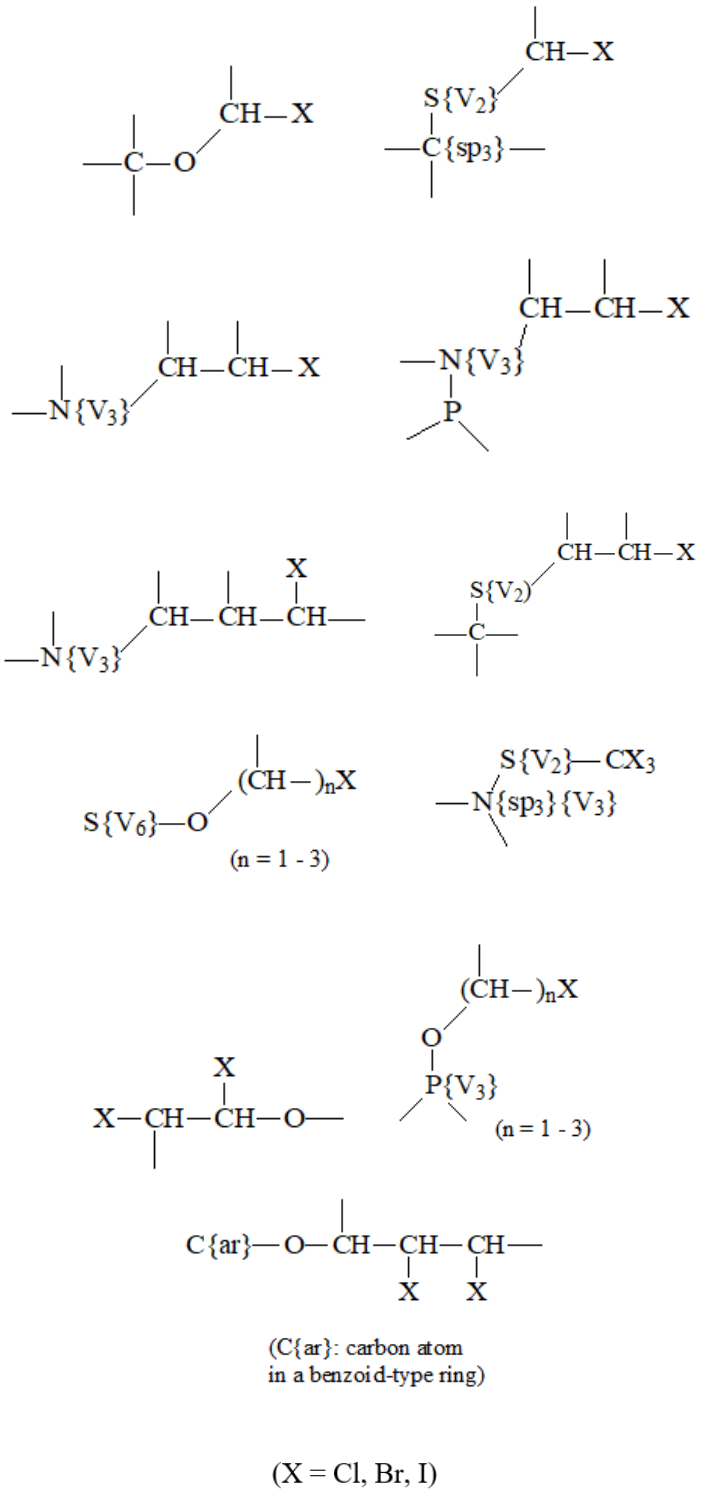
The following mechanism with metabolic activation can be expertly outlined in such cases, bearing in mind the proved formation of DNA adducts with propylene oxide [7]:

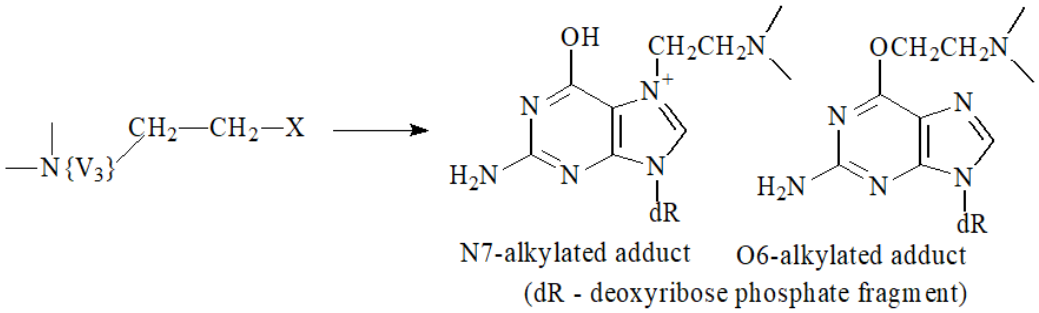


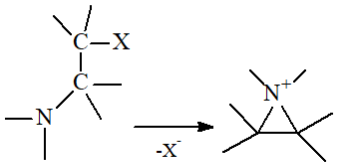
Scheme 2

Set of chemicals used for profile development	Monohaloalkanes
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1.Woo, Environ. Health Persp. **110** (2002), 75 – 87. 2. Ballering, Mutagenesis **9**(4) (1994), 387 – 389; DOI: 10.1093/mutage/9.4.387. 3. *Toxicology and Carcinogenesis Studies of Bromoethane (Ethyl Bromide) (CAS No. 74-96-4) in F344/N Rats and B6C3F₁ Mice (Inhalation Studies)*, NTP Technical Report Series No. 363, US Department of Health and Human Services, Public Health Service, National Institute of Health, October 1989; http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr363.pdf. 4. Guengerich, Jap. J. Toxicol. Environ. Health **43**(2) (1997), 69-82; http://sc.chat-shuffle.net/paper/uid:110003642293. 5. Warwick, Canc. Res. **23** (1963), 1315 -1333. 6. Sobol, Z., M. E. Emgel, E. Rubitski, W. W. Ku, J. Aubrecht, R. H. Schiestl, Genotoxicity Profiles of Commion Alkyl Halides and Esters with Alkylating Capability, Mutat. Res. 633 (2007), 80 – 94. 7. Solomon, Environ. Health Persp. **81** (1989), 19 – 22. 8. Strubel, Toxicol. Environ. Chem. **15**(1-2) (1987), 101 – 128.

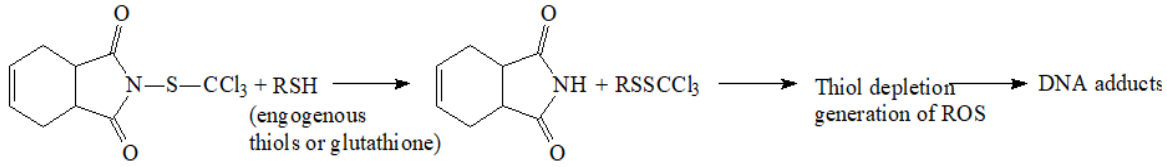
Individual profile/alert	
Name	Haloalkane Derivatives Containing Chain Heteroatom
Type of profile	Structural alert

Description/applicability domain	
Mechanism	**S_N2 Alkylation, nucleophilic substitution at sp3 carbon atom & Radical Generation of ROS by glutathione depletion (indirect)**
1. Compounds with halogen in β-position with respect to a heteroatom	



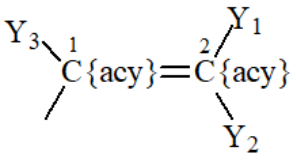
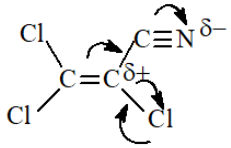


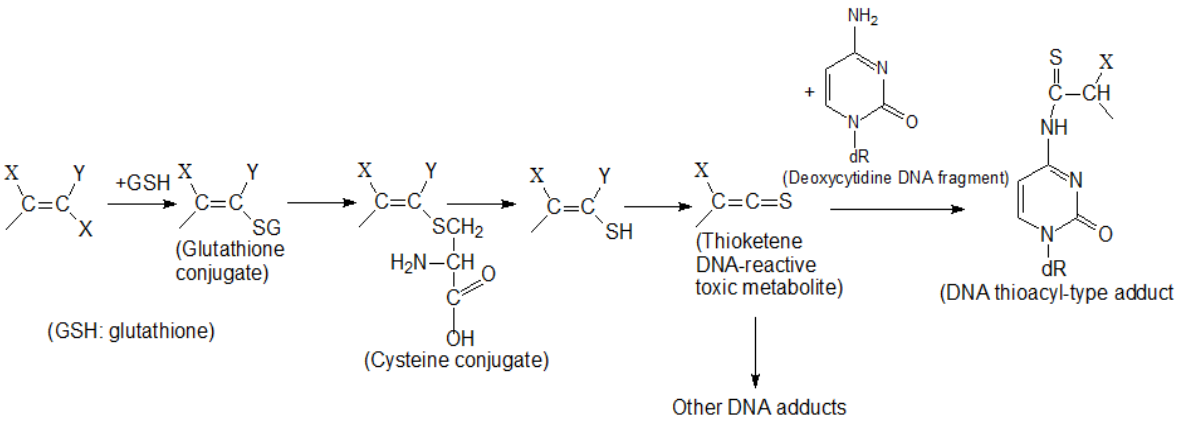
2. Compounds with halogen in α-position with respect to a heteroatom



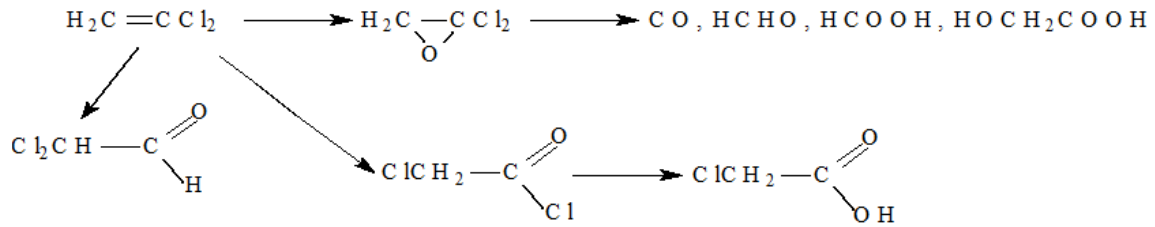
Set of chemicals used for profile development	Haloalkane Derivatives Containing Chain Heteroatom
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Kovacic, P., Medical Hypoth.**64** (2005), 104 - 111. 2. *Evidence on the Carcinogenicity of Technical Grade Bis(2-Chloro-1-Methylethyl) Ether*, Final November 1999 (Reproductive and Cancer Hazard Assessment Section Office of Environmental Health Hazard Assessment, California EPA; https://oehha.ca.gov/media/downloads/crnr/bcmeef_1.pdf,, last visited 09.2019. 3. Dacre, J. C., R. Beers, M. Goldman (Geo-Centers Inc. Newton Centre, MA), *Toxicology and Pharmacology of the Chemical Warfare Agent Sulfur Mustard – A Review* (1995); http://www.stormingmedia.us/72/7294/A729492.html 4. Theiss, J. C., Canc. Res. **39** (1979), 391-395. 5. B. Ringdahl, Pharmacol. Exper. Ther. **240 (**2) (1987), 370-375. 6. *Selected Chloroalkyl Ethers*, World Health Organization, International Programme on Chemical Safety, Environmental Health Criteria 201, (1998); http://www.inchem.org/documents/ehc/ehc/ehc201.htm 7. Van Duuren, Ann. New York Acad. Sci **163** Biological Effects of Alkylating Agents No. 2 (1969), 633 – 650; DOI: 10.1111/j.1749-6632.1969.tb24883.x. 8. Ruiz, M. J., Mutat. Res. **390** (1997), 245 – 255. 9. DeBaun, J. R., Xenobiotica **4**(2) (1974), 101-119. 10. D. Morte, R., Boll. Soc. Ital. Biol. Sper. **70**(8-9) (1994), 185 – 192

	(Abtsract); http://www.ncbi.nlm.nih.gov/pubmed/7893475 11. CCRIS: Mephalan, Toxicology Data Network, U.S. National Library of Medicine; https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+ccris:@term+@rn+148-82-3 12. CCRIS: Chlomaphazine, Toxicology Data Network, U.S. National Library of Medicine; https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+ccris:@term+@rn+494-03-1 13. CCRIS: Uracil Mustard, Toxicology Data Network, U.S. National Library of Medicine; https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+ccris:@term+@rn+66-75-1 14. CCRIS: Acrylic Acid, 2-Bromoethyl Ester, Toxicology Data Network, U.S. National Library of Medicine; https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+ccris:@term+@rn+4823-47-6

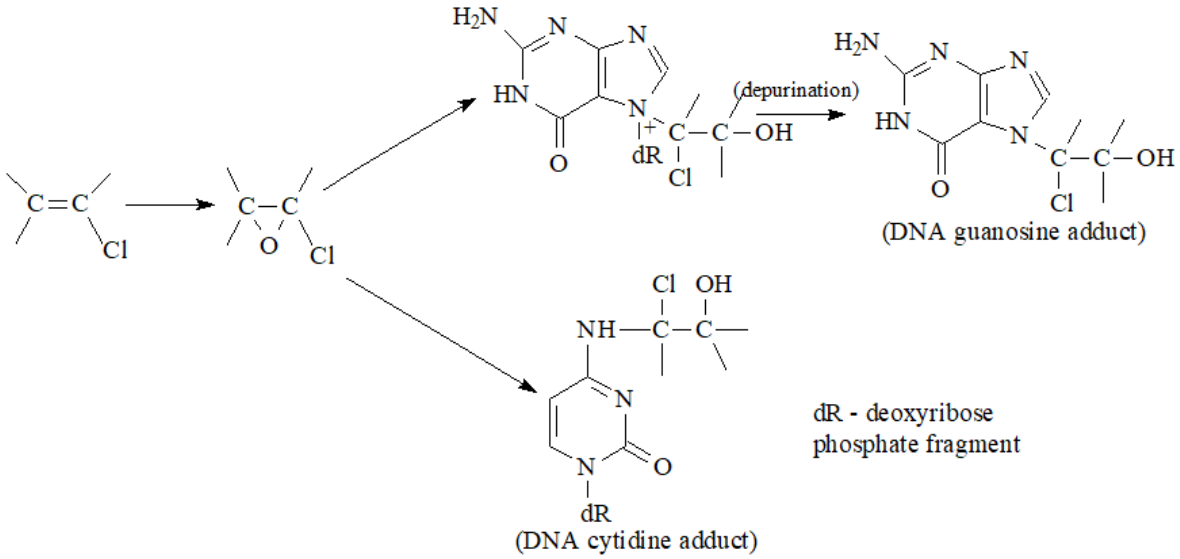
Individual profile/alert	
Name	Haloalkene Derivatives with Electron-Withdrawing Groups
Type of profile	Structural alert
Description/applicability domain	 Y_2 can be $–NO_2$ or –CN or **-C=C-** or Cl or Br or -C(O)O- (attached *via* the carbon of carbonyl group C(O)), or -C(O)C (attached *via* the carbon of carbonyl group C(O)); Y_3 is Cl or Br or H C(O) corresponds to carbonyl group C=O No $–SO_3H$ or -COOH groups attached to the C_1-atom;
Mechanism	**S_N2 Direct alkylation or alkylation by metabolically formed epoxides & A_N2 Thioacylation *via* nucleophilic addition after thioketene formation**
1. Haloalkenes containing halogen(s) and other electron-withdrawing group(s) (EWG). 	



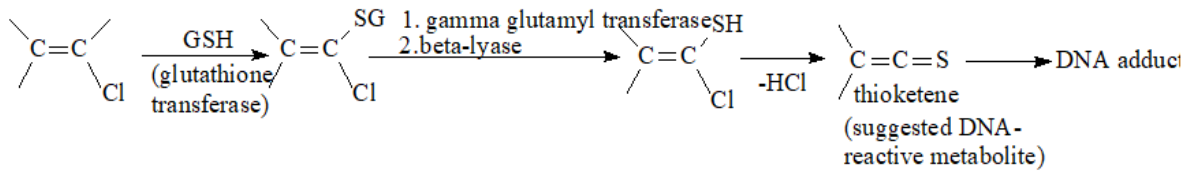
2. Vinyl-type haloalkenes, not containing other EWGs

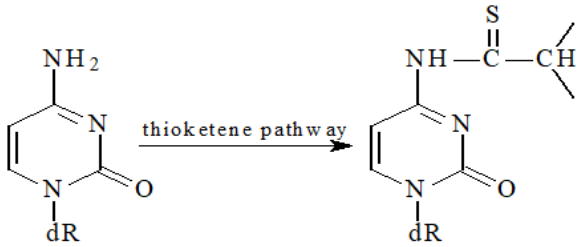


3. Formation of epoxide intermediate that binds covalently to DNA *via* electrophilic mechanism of alkylation towards the biological macromolecule:



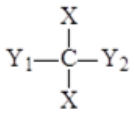
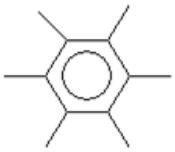
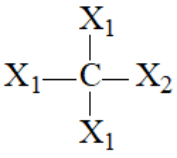
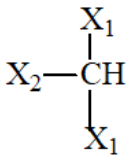
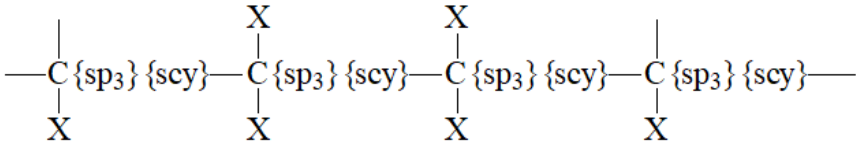
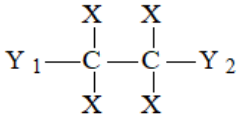
4. Glutathione or thiol activation pathway. In this case, the formation of reactive product that binds to DNA *via* electrophilic mechanism [11] takes place:

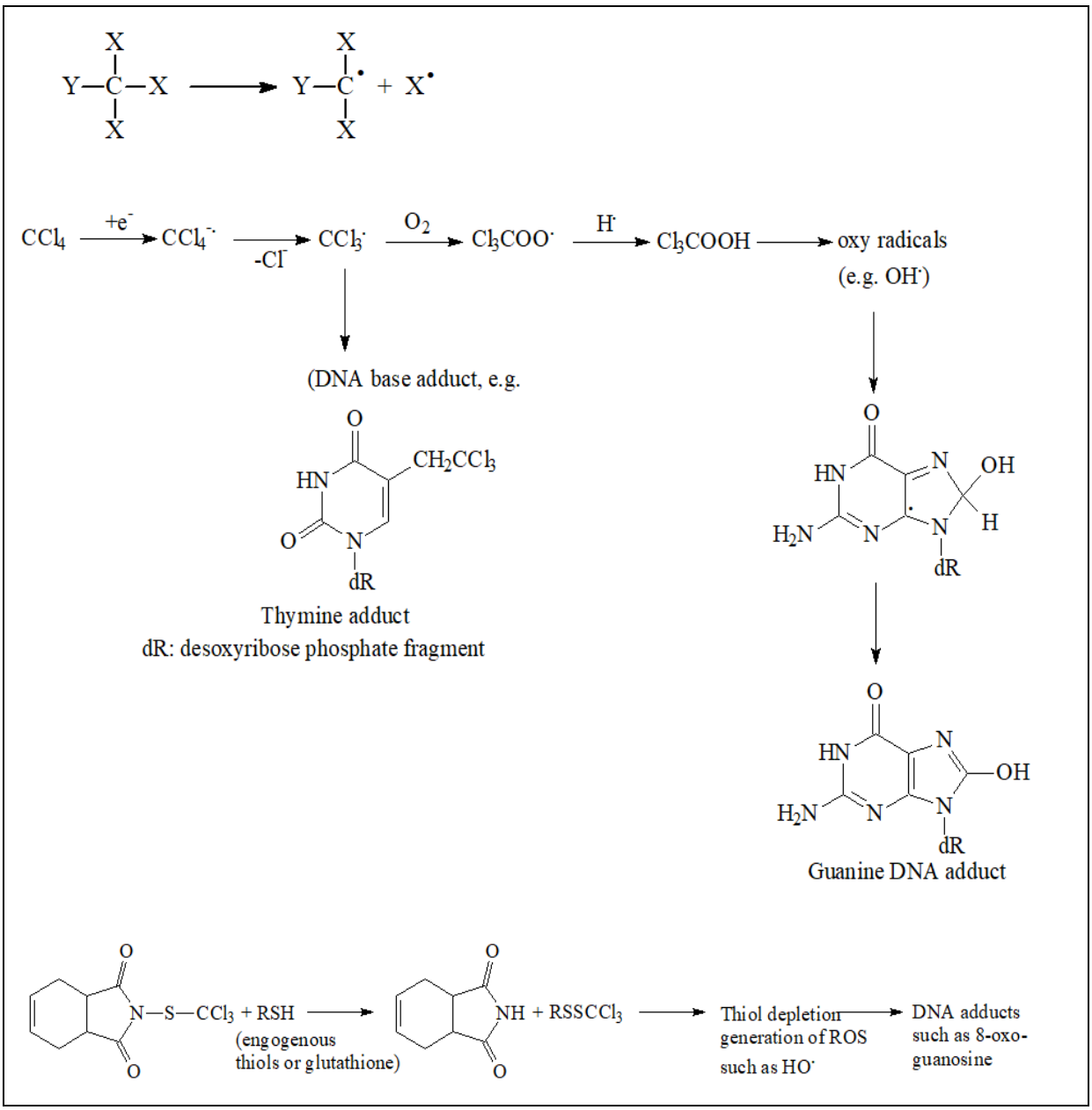


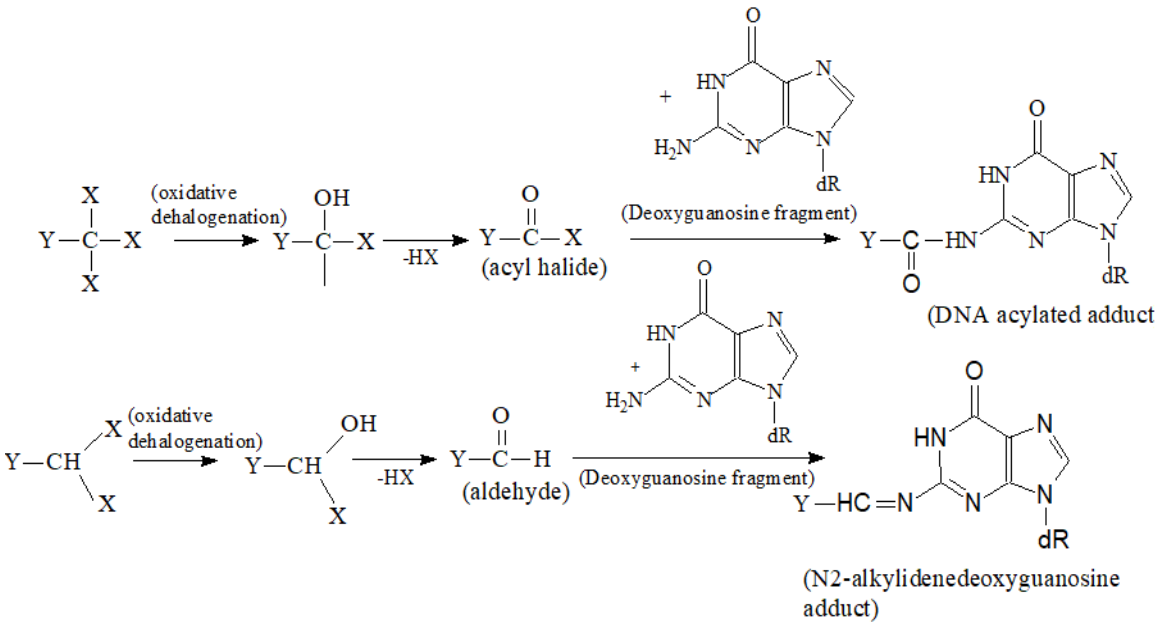


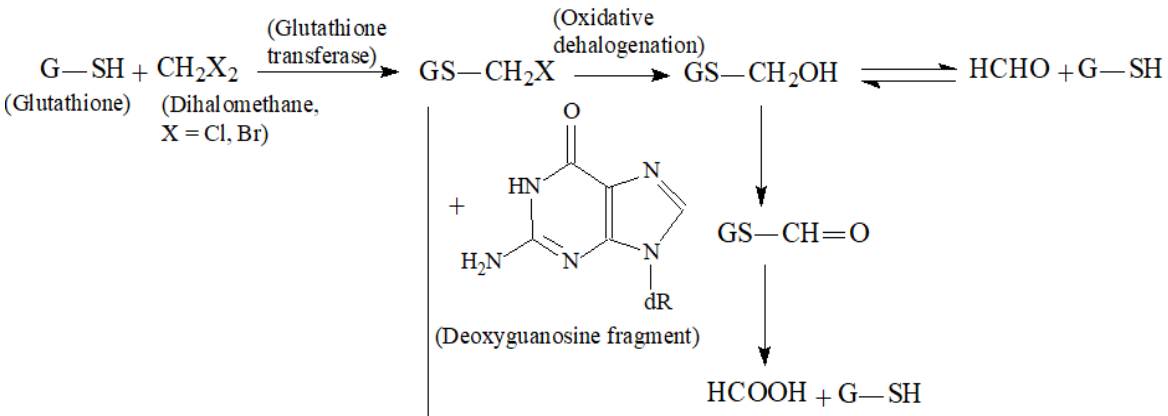
(dR - deoxyribose phosphate fragment)

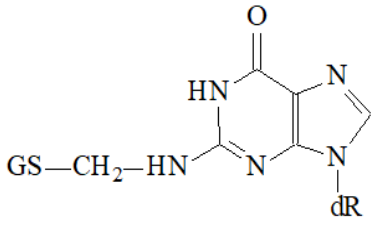
Set of chemicals used for profile development	Haloalkene Derivatives with Electron-Withdrawing Groups
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Woo, Y. T., Environ. Health Persp. **110** (Suppl. 1) (2002), 75 - 87. 2. Kim, D., Drug Metab. Dispos. **34**, 2006, 2020 – 2027. 3. Decant, W., Environ. Health Persp. **88** (1990), 107 – 110. 4. Muller, M., Chem. Res. Toxicol. **11**(5) (1998), 464 – 470; DOI: 10.1021/tx9701440. 5. *Vinyl Chloride, An Annotated Bibliography with Emphasis on Genotoxicity and Carcinogenicity* (Prepared by Dr. Michael F. Salamone and Dr. Gary Westlake), Ontario Ministry of Environment, September 1998; http://www.ene.gov.on.ca/stdprodconsume/groups/lr/@ene/@resources/documents/resource/std01_079011.pdf 6. Lijinsky, W., Teratog. Carcinog. Mutag. **1** (1980), 259 – 267. 7. *Trichloroethylene*, International Programme on Chemical Safety, Environmental Health Criteria 50; http://www.inchem.org/documents/ehc/ehc/ehc50.htm#SectionNumber:5.3 8. Fahrig, R., Mutat. Res. 340 (1995), 1 – 36. 9. *Vinylidene Chloride* International Programme for Chemical Safety, Environmental Health Criteria 100; http://www.inchem.org/documents/ehc/ehc/ehc100.htm#SubSectionNumber:6.1.4 10. *Toxicological Profile for Hexachlorobutadiene*, US Dept. of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry (May 1994); http://www.atsdr.cdc.gov/toxprofiles/tp42.pdf 11. Muller, M., Chem. Res. Toxicol. **11**(5) (1998), 464 – 470; DOI: 10.1021/tx9701440. 12. Strubel, K., Toxicol. Environ. Chem. **15**(1-2) (1987), 101 – 128. 13. Rannug, U., Chem.-Biol. Interact. **12** (1976), 251 – 263. 14. Mucochloric Acid, PubChem Open Chemistry Database, U.S. National Library of Medicine; https://pubchem.ncbi.nlm.nih.gov/compound/Mucochloric_acid#section=Top 15. Dichlorvos, ChemPlus, A Tooxnet Database, U.S. National Library of Medicine; https://chem.nlm.nih.gov/chemidplus/rn/62-73-7 16. Bucher, J. R., *NTP Technical Report on Toxicity Studies of β-Bromo-β-Nitrostyrene (CAS No. 7166-19-0) Administered by Gavage to F344/N Rats and B6C3F Mice*, NIH Publication, August 1994; https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox040.pdf

Individual profile/alert	
Name	Geminal Polyhaloalkane Derivatives
Type of profile	Structural alert
Description/applicability domain	 X can be Cl, Br, I; Y_1 can be X or H; Y_2 can be -H, -CH-O-, S{V2}, -CN, -CHO, $-CH_2X$, -C(O)X, $-CH_3$, -C(O)-O- (carboxyl group attached *via* C-atom); Y_2 can be also:  (no electron-withdrawing halogens or $-CF_3$ attached; no more than two substituents in the phenyl ring)  (X_1 = F or Cl; X_2 = Br or I)  X_1 is F or Cl; X_2 is Cl or Br  X= Cl, Br  (Y_1 is C or H or combinations or S{V2}; Y_2 is C or H; X is Cl or Br
Mechanism	**S_N2 Nucleophilic substitution at sp3 carbon atom after thiol (glutathione) conjugation, Radical ROS generation, S_N2 Acylation involving a leaving group after metabolic activation & A_N2 Shiff base formation by aldehyde formed after metabolic activation**

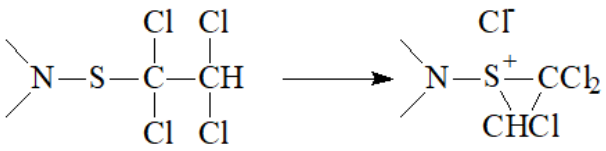

Y—C(X)(X)—X → Y—C•(X)(X) + X•
CCl4 +e- CCl4•- -Cl- CCl3• O2 Cl3COO• H• Cl3COOH → oxy radicals (e.g. OH•)
(DNA base adduct, e.g.
CH2CCl3
dR
Thymine adduct
dR: desoxyribose phosphate fragment
OH
H
Guanine DNA adduct
N—S—CCl3 + RSH
(engogenous thiols or glutathione)
NH + RSSCCl3
Thiol depletion
generation of ROS such as HO•
DNA adducts such as 8-oxo-guanosine

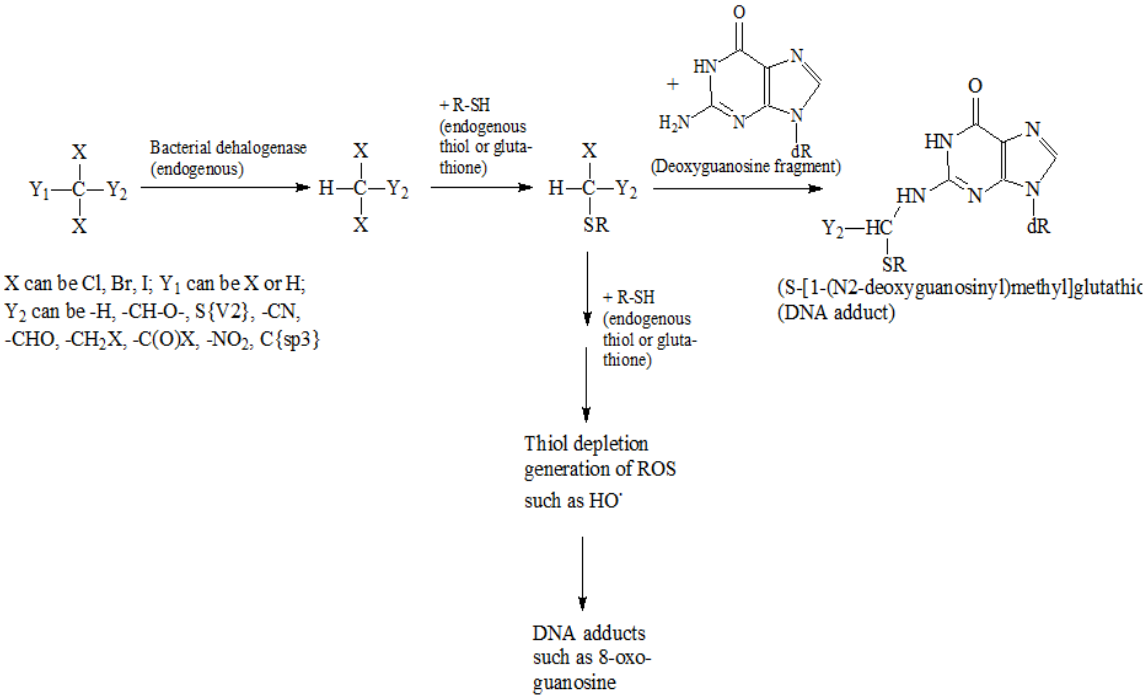






(S-[1-(N2-deoxyguanosinyl)methyl]glutathione (DNA adduct)





Set of chemicals used for profile development	Geminal Polyhaloalkane Derivatives
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Strubel, K., Toxicol. Environ. Chem. **15**(1-2) (1987), 101 – 128. 2. *Chemical Carcinogenesis Research Information System (CCRIS)*; http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?CCRIS 3. Longstaff, E., *Toxicol. Lett.*, **1978**, **2**(1), 1 – 4. 4. Anders, M. W., Environ. Health Persp. **96** (1991), 185 – 191. 5. Dodd, D.E., *Inhal. Toxicol.*, **1997**, 9(2), 111 – 131. 6. A.D. Mitchell, Genetic Toxicity Evaluation of Iodotrifluoromethane (CF_3I), Vol. 1. Results of Salmonella typhimurium Histidine Reversion Assay. Govt. Reports Announcements & Index (GRA & I) Issue 06, 1996). 7. CCRIS: Trifluoroiodomethane RN: 2314-97-8, Toxicology Data Network, U.S. National Library of Medicine**;** http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+ccris:@term+@rn+2314-97-8. 8. CCRIS: 1,1,1-Trichloroethane CASRN: 71-55-6, Toxicology Data Network, U.S. National Library of Medicine**;** http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+ccris:@term+@rn+71-55-6. 9. Schrader, T.J., *Mutat. Res.*, **1998**, **413**(2), 159 - 168. 10. Mortelmans, K., *Environ. Mutagen.*, **1986**, 8 (Suppl. 7), 1 - 119. 11. Hosey, K. M. Quinn, J. Environ. Protection **3** (21012), 902 – 914. 12. Captafol CASRN: 2425-06-1, CCRIS, Toxicology Data Network, U.S. National Library of Medicine; http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+ccris:@term+@rn+2425-06-1 . 13. Barrueco, C., Mutagen. **3**(6) (1988), 467 – 480. 14. Sims, J. L., J. M. Suflita, H. H. Russel, Reductive Dehalogenation of Organic Contaminants in Soils and Ground Water, EPA/540/4-90/054, January 1991, 1 –

12.
15. Ruiz, M. J., Mutat. Res. **390** (1997), 245 – 255.
16. DeBaun, J. R., Xenobiotica **4**(2) (1974), 101 - 119.
17. D. Morte, Boll. Soc. Ital. Biol. Sper. **70**(8 - 9) (1994), 185 – 192 (Abtsract); http://www.ncbi.nlm.nih.gov/pubmed/7893475).
18. Bagchi, D., Toxicol. **104** (1995), 129 – 140.
19. Kovacic, P., Current Medic. Chem. **8**, 2001, 773 – 796.
20. Wiseman, H., Biochem. J. **313** (1996), 17 – 29.
21. Gerardo, D. C., Chem.-Biol. Interact. (1994), 13 – 22.
22. *Public Health Goal for Carbon Tetrachloride in Drinking Water*, Office of Environmental Health Hazard Assessment, California EPA, pesticide and Environmental Toxicology Section, September 2000; http://oehha.ca.gov/water/phg/pdf/carbtet.pdf.
23. Di Ilio, C., Biochem. Pharmacol. **52** (1996), 43 – 48.
24. Yasuo, K., Mutat Res. **58**(2-3) (1978), 143 - 150; http://www.sciencedirect.com/science/article/pii/0165121878900034.
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27. Chiu, C. W., L. H. Lee, C. Y. Wang, G. T. Bryan, *Mutagenicity of Some Commercially Available Nitro Compounds for Salmonella Typhimurium*, Mutat Res. **58**(1) (1978), 11 – 22; http://www.biomedsearch.com/nih/Mutagenicity-some-commercially-available-nitro/362191.html.
28. Wang, M., Chem. Res. Toxicol. **13**(11) (2000), 1149 – 1157; http://pubs.acs.org/doi/abs/10.1021/tx000118t.
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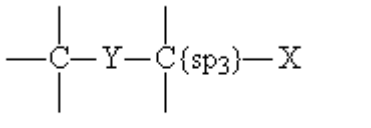
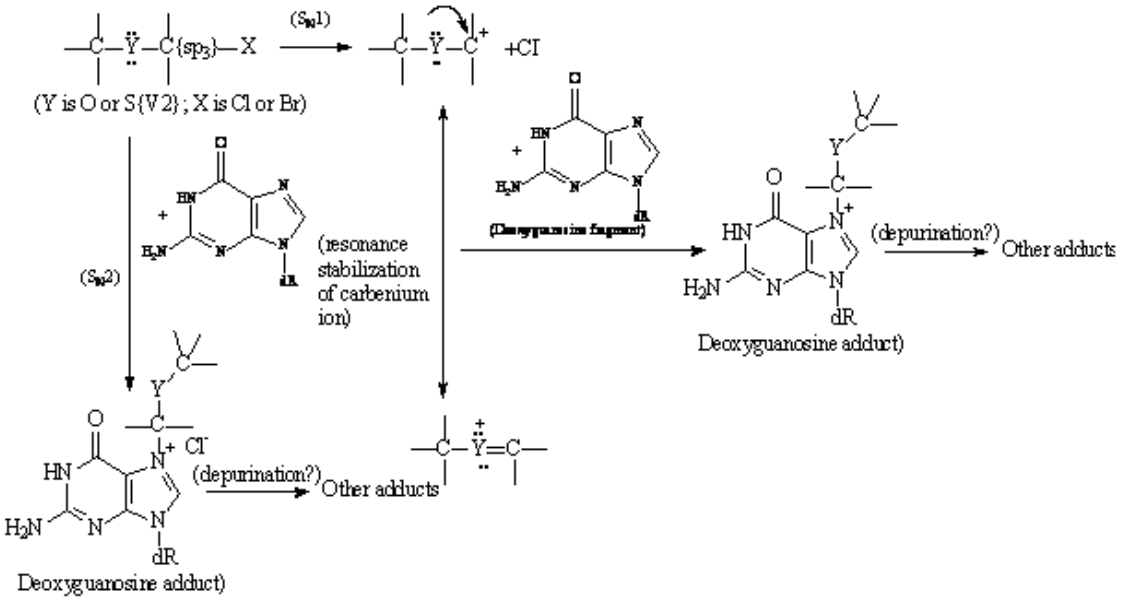
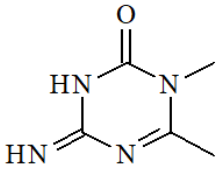
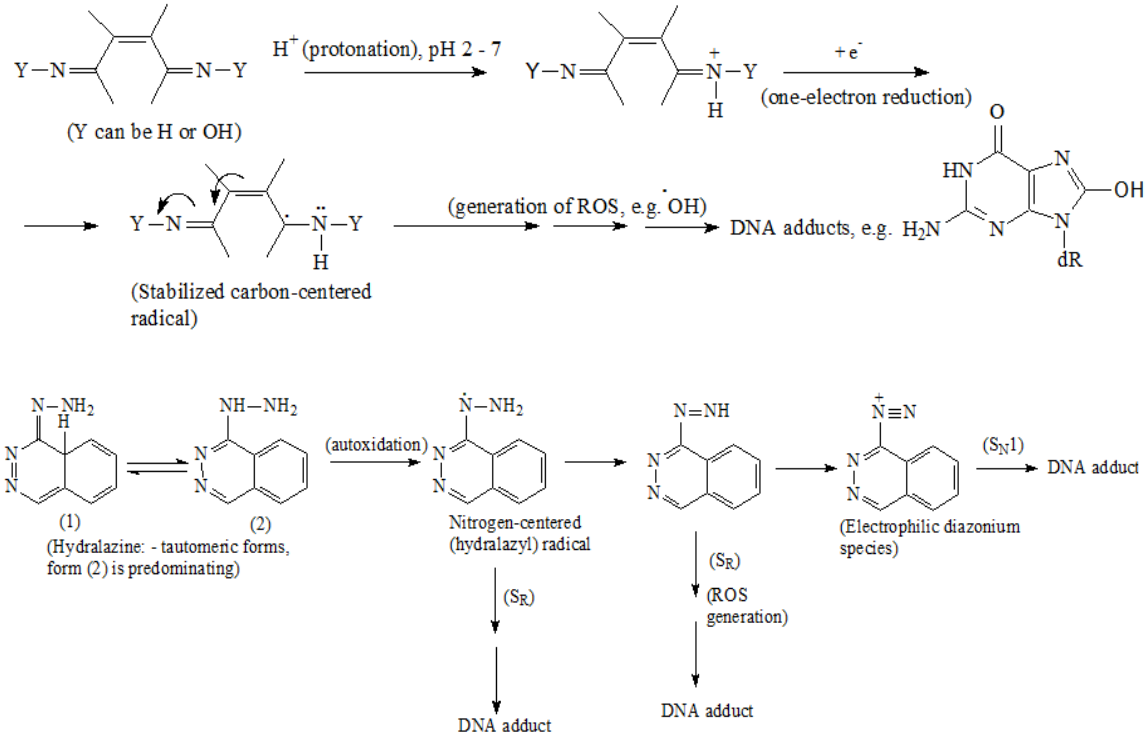
30. Bernard, Br. K., Inter. J. Toxicol. **19** (2000), 43 – 61.
31. Mejer, J., Chem.-Biol. Interact. **31** (1980), 247 – 254.
32. Morita, T., Mutat. Res. **802** (2016), 1 – 29.
33. Sato, T., The Science of Total Environment **46** (1985), 229 – 241.

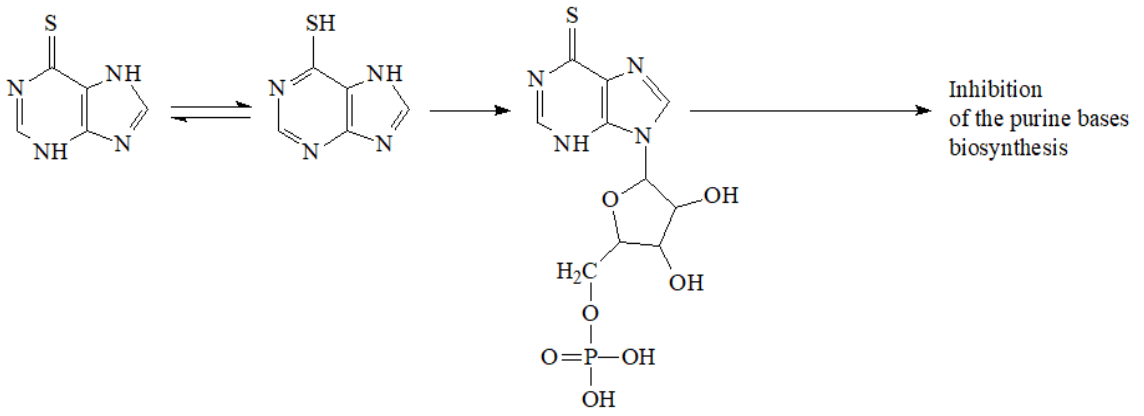
Individual profile/alert	
Name	Alpha-Haloethers
Type of profile	Structural alert
Description/applicability domain	 (Y is O or S(V2); X is Cl or Br
Mechanism	**S_N1 after carbenium ion formation and S_N2 at an sp3 carbon atom**
The following mechanistic schemes can be expertly outlined:	



Set of chemicals used for profile development	Alpha-Haloethers
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. *Selected Chloroalkyl Ethers*, World Health Organization, International Programme on Chemical Safety, Environmental Health Criteria 201, (1998); http://www.inchem.org/documents/ehc/ehc/ehc201.htm, last visisted 09.2019 2. Van Duuren, Ann. New York Acad. Sci **163,** No. 2 (1969), 633 – 650; DOI: 10.1111/j.1749-6632.1969.tb24883.x. 3. Fishbein, Mutat. Res. **32** (1976), 267 – 308). 4. Zajdela, Canc. Res. **40** (1980), 352 – 356. 5. Enoch, ATLA **39** (2011), 131 – 145. 6. Enoch, Crit. Rev. Toxicol. **41**(9) (2011), 783 – 802. 7. Van Duuren, Ann. New York Acad. Sci **534** (1988), 620 – 634.

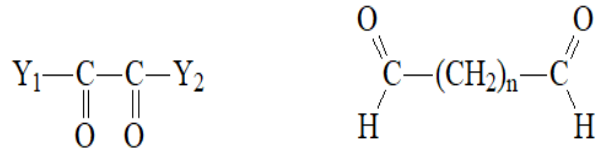
Individual profile/alert	
Name	Specific Imine and Thione Derivatives
Type of profile	Structural alert

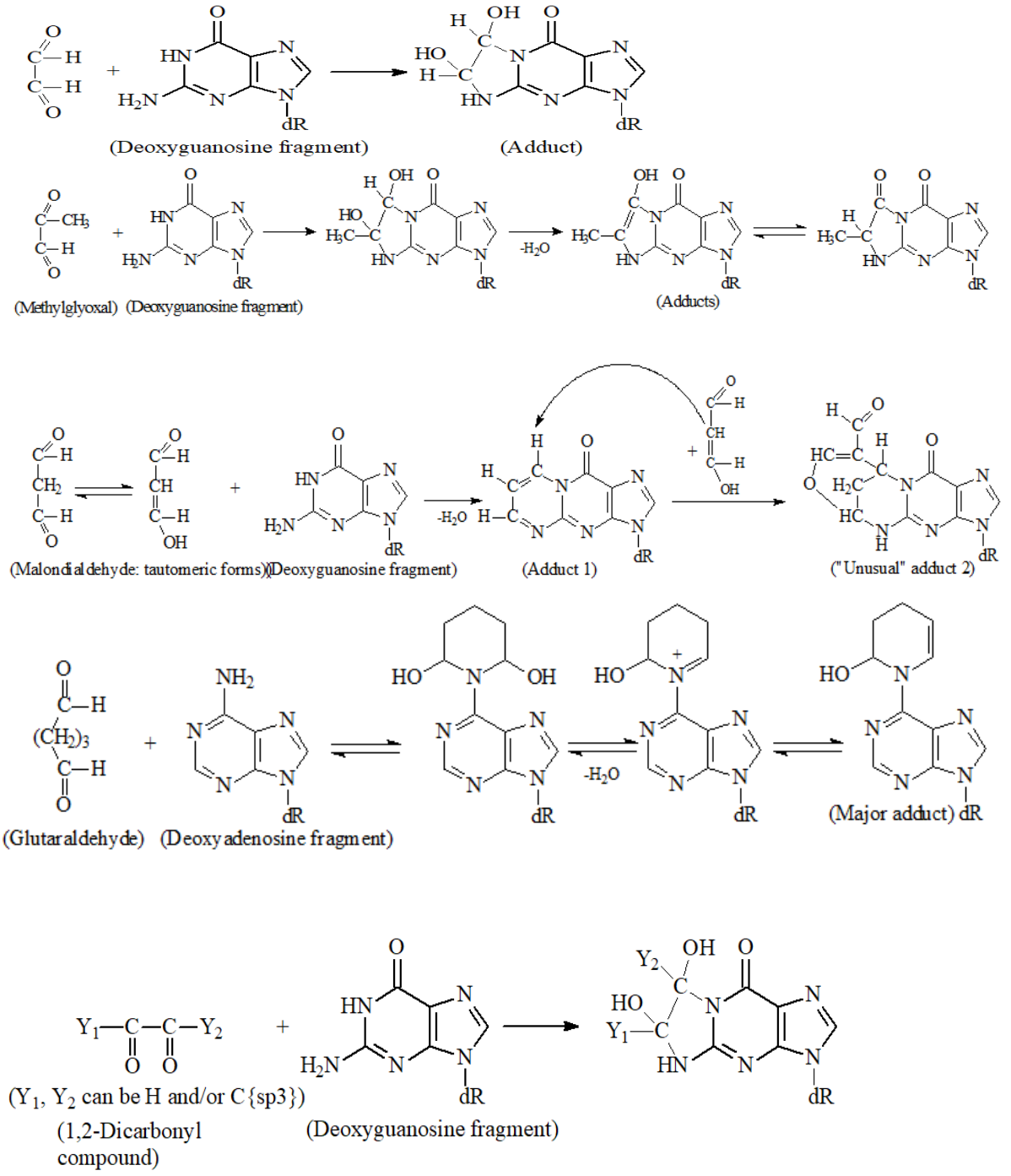
Description/applicability domain	(1) —C{scy}=C{scy}—C{scy}=N{acy}{V_3}— (2) —C{scy}=N{scy}{V_3}—C{scy}=S (3) —N{scy}{V_3}=N{scy}{V_3}—C{scy}=N{acy}{V_3}— {scy} - cyclic atom; {acy}: acyclic atom; V - valency (4)  (5) 
Mechanism	**S_R ROS formation , S_N1 Nucleophilic substitution on diazonium ion & Non-specified Incorporation into DNA/RNA, due to structural analogy with nucleoside bases**
	

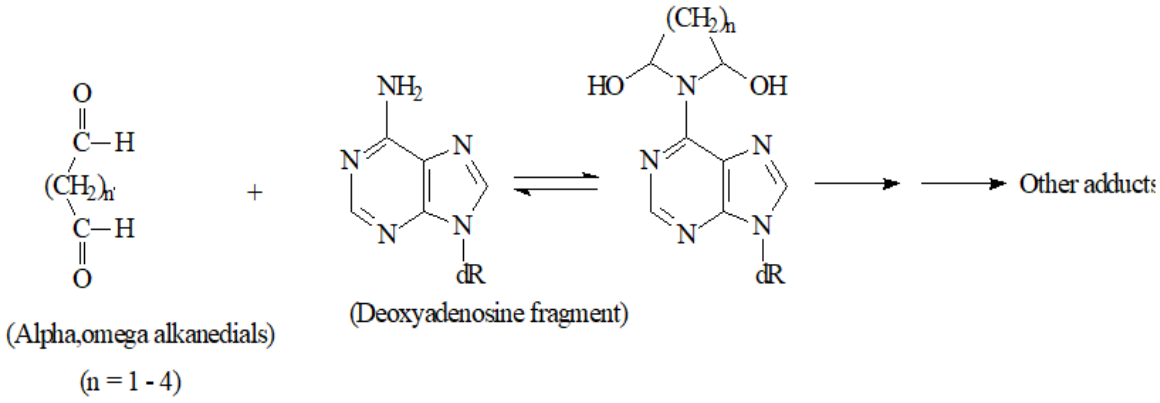


(6-Mercaptopurine ribonucleotide
(Thioinosinic acid))

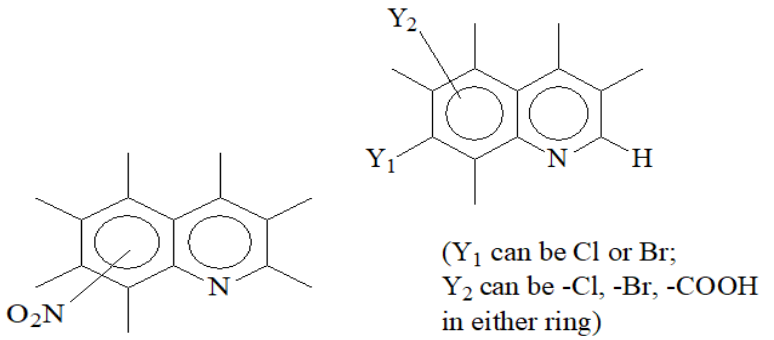
Set of chemicals used for profile development	Specific Imine and Thione Derivatives
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. *1,4-Benzoquinone Dioxime*, IARC Monographs, Vol. 71, 1999; ISBN-13 (PDF): 978-92-832-1571-4. 2. Westmoreland, C., Environ. Molec. Mutag. **19** (1992), 71 – 76. 3. Niufar, N. N., Rev. Soc. Quimica de Mexico **46**(4) (2002), 307 – 312. 4. Sinha, B., Biochem. Pharmacol. **32**(22) (1983), 3279 – 3284. 5. Yamamoto, K., Biochem. Pharmacol. **41** (6/7) (1991), 905 – 914. 6. Chlopkiewicz, B., Toxicol. Lett. **110** (1999), 203 – 207. 7. Benedict, W. F., Canc. Res. **37** (1977), 2209 – 2213. 8. Seino, Y., Canc. Res. **38** (1978), 2148 – 2156. 9. Pommer, Y., Cold Spring Harbor Press, Ed. By M. L. DePamphilis, 1 – 28; http://discover.nci.nih.gov/pommier/ReplicationInhibitorsText.pdf. Last visited 09.2019. 10. Christman, J. K., Oncogene **21** (2002), 5483 – 5495. 11. Kelecsenyi, Z., Mutag. **15**(1) (2000), 25 – 31.

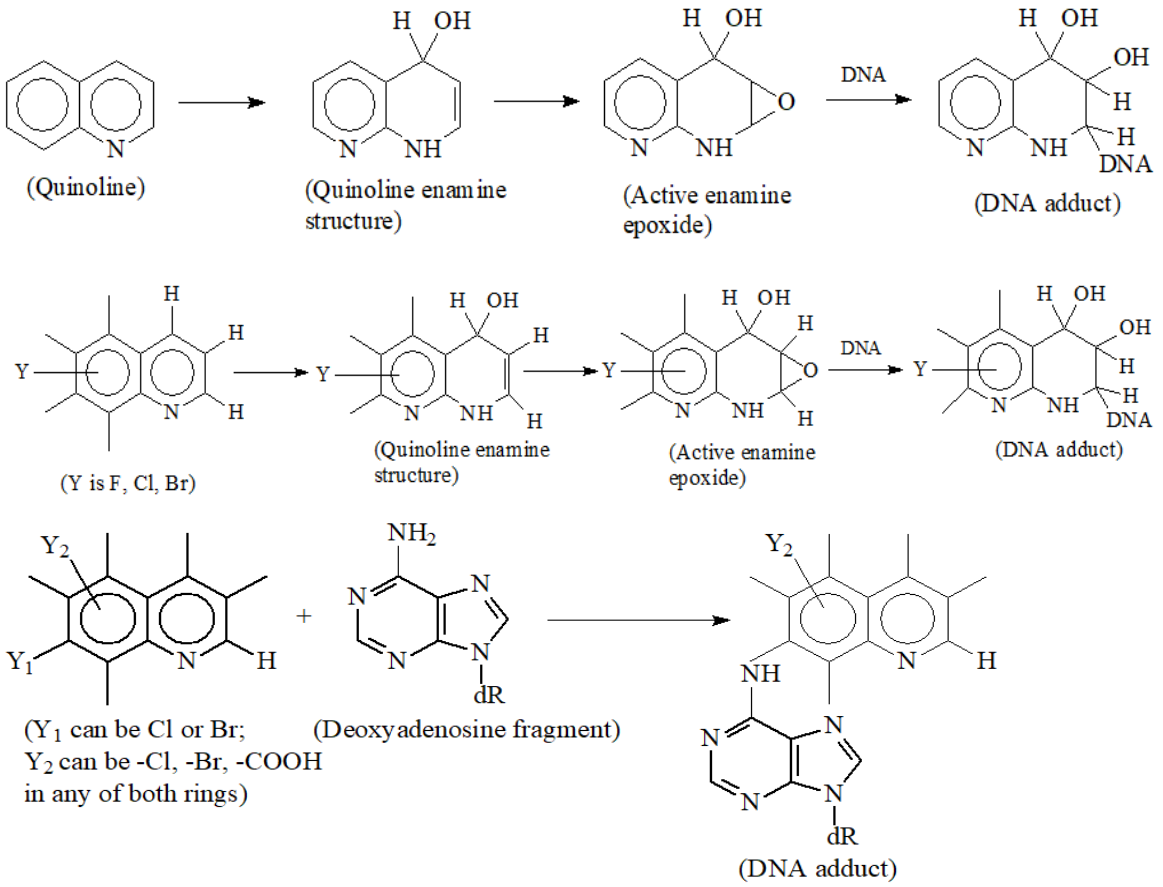
Individual profile/alert	
Name	Dicarbonyl Compounds
Type of profile	Structural alert
Description/applicability domain	 (Y_1, Y_2 can be H and/or C{sp3}) (n = 1 - 4)
Mechanism	**A_N2 Shiff base formation**


(Deoxyguanosine fragment)
(Adduct)
(Methylglyoxal)
(Deoxyguanosine fragment)
(Adducts)
(Malondialdehyde: tautomeric forms)
(Deoxyguanosine fragment)
(Adduct 1)
("Unusual" adduct 2)
(Glutaraldehyde)
(Deoxyadenosine fragment)
(Major adduct)
(Y1, Y2 can be H and/or C{sp3})
(1,2-Dicarbonyl compound)
(Deoxyguanosine fragment)



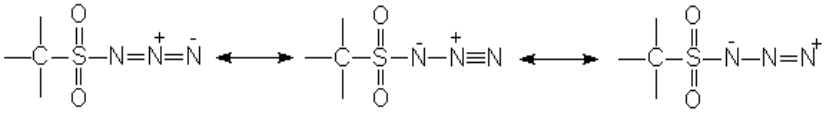
Set of chemicals used for profile development	Dicarbonyl Compounds
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
qReferences	1. Bjeldanes, L. F., Mutat. Res. **67** (1979), 367 – 371. 2. Dorado, L., Mutat. Res. **269** (1992), 301 – 306. 3. Mellado, J. M. R., Mutat. Res. **304** (1994), 261 – 264. 4. Shapiro, R., Biochem. **5**(9) (1966), 2799 – 2807). 5. Frishmann, M., Chem. Res. Toxicol. **18** (2005), 1586 – 1592). 6. More, S. S., J. Agric. Food Chem. **60** (2012), 3311 – 3317. 7. Marnett, L. J., J. Am. Chem. Soc. **108** (1986), 1348 – 1350). 8. Olsen, R., Chem. Res. Toxicol. **20** (2007), 965 – 974.

Individual profile/alert	
Name	Quinoline Derivatives
Type of profile	Structural alert
Description/applicability domain	 (Y_1 can be Cl or Br; Y_2 can be -Cl, -Br, -COOH in either ring)
Mechanism	**S_N2 Direct acting epoxides formed after metabolic activation & S_N2 at an activated carbon atom**

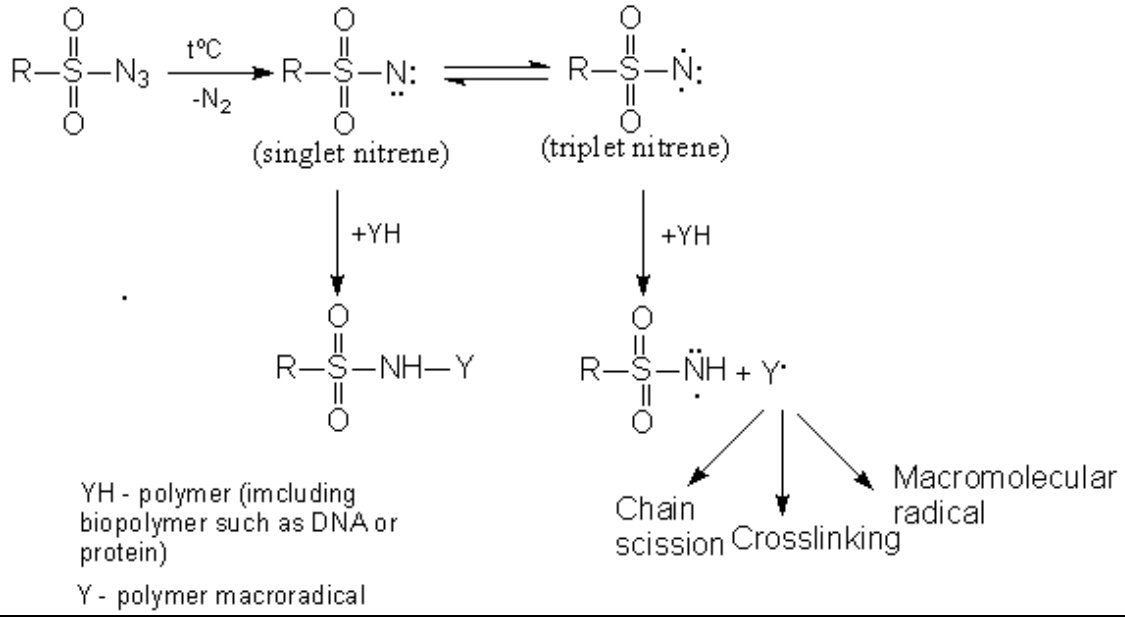


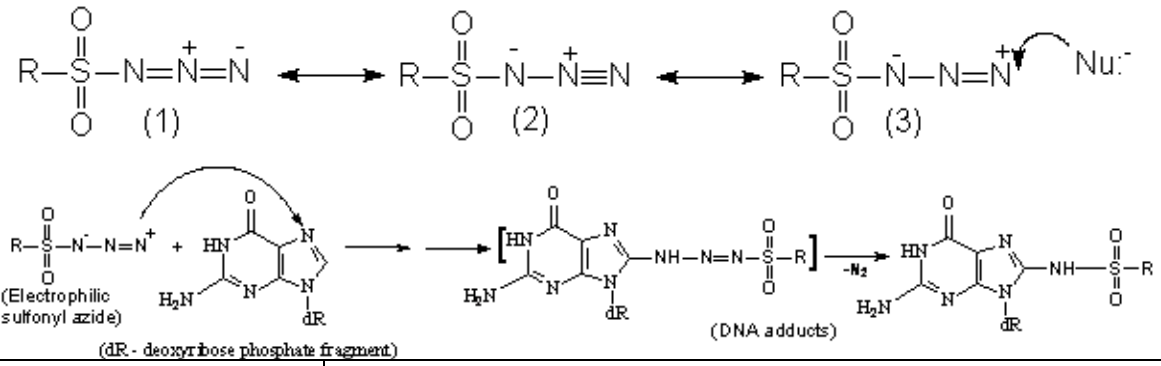
Set of chemicals used for profile development	Quinoline Derivatives
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Nagao, M., Mutat. Res. **42** (1977), 335 – 342. 2. Willems, M. I., Mutat. Res. **278** (1992), 227 – 236. 3. Miyata, Y., Muitat. Res. **414** (1998), 165 - 169. 4. Suzuki, T., J. Health Sci **53**(3) (2007), 325 – 328. 5. Reigh, G., Carcinog. **17**(9) (1996), 1989 – 1996. 6. *Quinoline* (*CASRN 91-22-5*) Integrated Risk Information System, US-EPA; https://www.epa.gov/iris, last visited 10.2019 2. Arima, Y., Ch. Nishigori, T. Takeuchi, Sh. Oka, K. Morimoto, *4-Nitroquinoline 1-Oxide Forms 8-Hydroxydeoxyguanosine in Human Fibroblasts through Reactive Oxygen Species*, Toxicol. Sci **91**(2) (2006), 382 – 392. 3. *4-Hydroxylaminoquinoline-1-Oxide*, Toxicology Data Network, US National Library of Medicine; Okabayashi, T., Mutagenic Activity of 4-Hydroxylaminoquinoline 1-Oxide, Chem. Pharm. Bull. (Tokyo), 10 (1962), 1127-1128. 4. Ferguson, L. R., W. A. Denny, Genotoxicity of Non-Covalent Interactions: DNA Intercalators (Review),

Mutat. Res. **623** (2007), 14 – 23.
5. Snyder, R. D., Possible Structural and Functional Determinants Contributing to the Clastogenicity of Pharmaceuticals, Environ. Molec. Mutag. **51** (2010), 800 – 814.
6. Snyder, R. D., D. Ewing, L. B. Hendry, DNA Intercalative Potential of Marketed Drugs Testing Positive in In Vitro Cytogenetics Assays, Mutat. Res. 609 (2006), 47 – 59.
7. Shubber, E. K., D. J. Kram, J. R. Williams, *Comparison of the Ames Assay and the Induction of Sister Chromatid Exchanges: Results with Ten Pharmaceuticals and Five Selected Agents*, Cell Biol. Toxicol. **2**(3) (1986), 379 – 399.

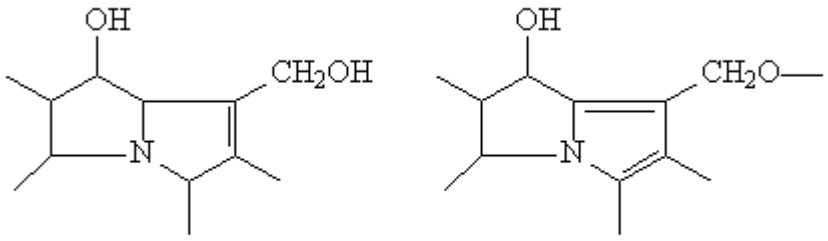
Individual profile/alert	
Name	Sulfonyl Azides
Type of profile	Structural alert
Description/applicability domain	
Mechanism	**S_N1 Nitrenium ion formation**

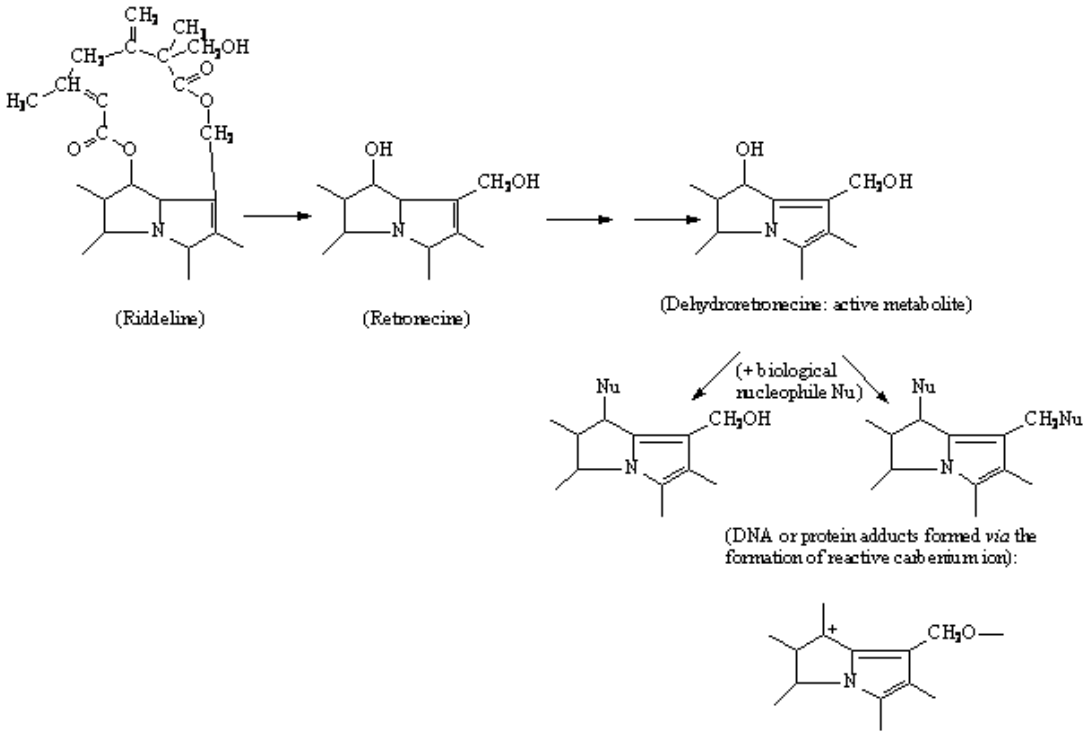
The following mechanistic schemes can be expertly outlined:





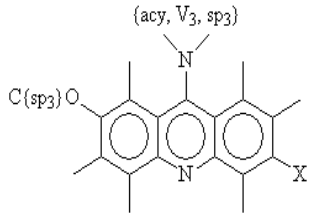
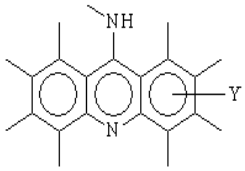
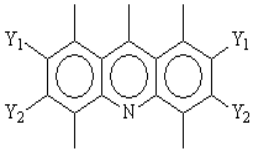
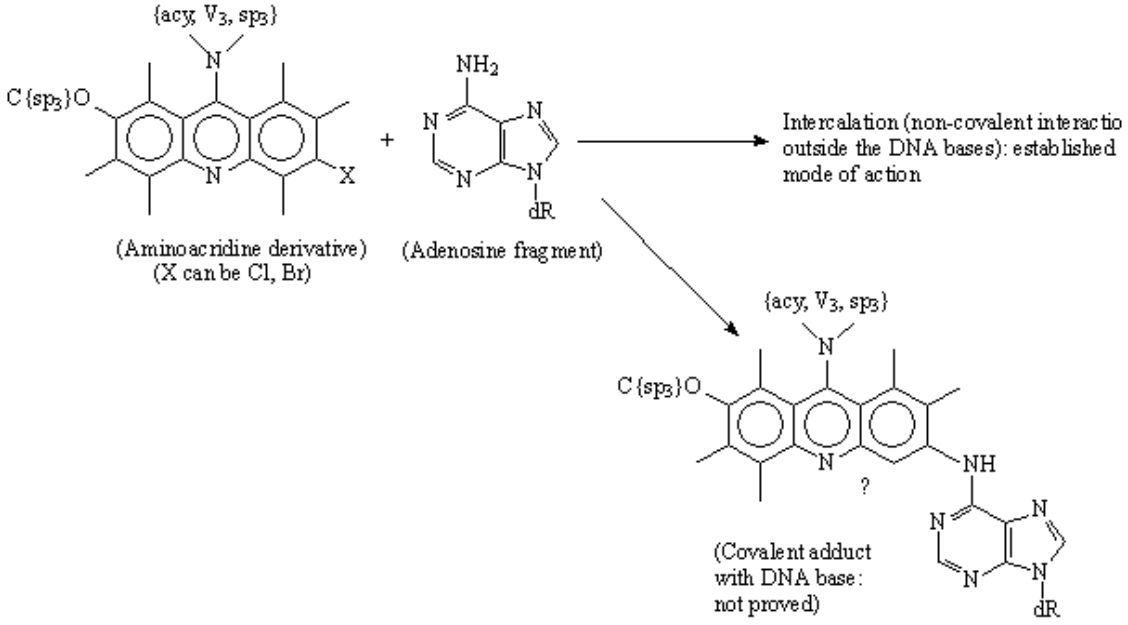
Set of chemicals used for profile development	Sulfonyl Azides
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Clarke, J. Biol. Chem. **261**(22), 1986, 10063 – 10072. 2. *22778 4,4'-Oxydibenzenesulfonyl Azide*, Opinion of the Scientific Committee on Food on the 11th Additional List of Monomers and Additives for Food Contact Materials, Scientific Committee on Food, European Commission, Health&Consumer Protection Directorate General, 13 November 2000; https://ec.europa.eu/food/sites/food/files/safety/docs/sci-com_scf_out76_en.pdf, last visited 09.2019. 3. Li, IPR 28th Annual Symposium Waterloo, May 16, 2006; http://www.ipruw.com/publications/2006/oral_pres/BobLi.pdf. 4. Merkx, R., *Application of Azides in Chemoselective Amidation Reactions*, PhD Thesis; ISBN: 978-90-393-5025-6. 5. Brase, Angew. Chem. Int. Ed. **44** (2005), 5188 – 5240.

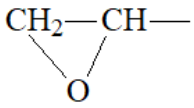
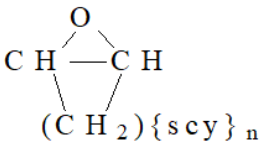
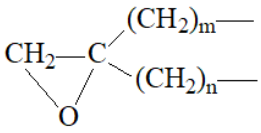
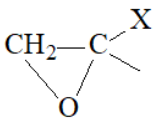
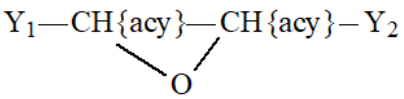
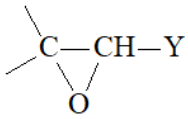
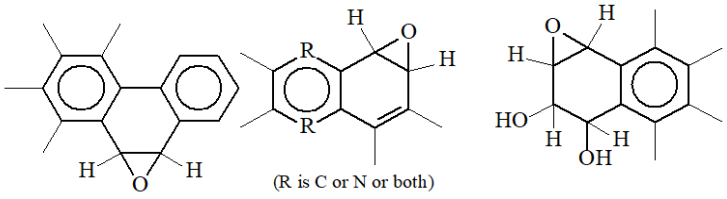
Individual profile/alert	
Name	Pyrrolizidine Derivatives
Type of profile	Structural alert
Description/applicability domain	
Mechanism	**S_N1 Nucleophilic attack after carbenium ion formation**
The following scheme of bioactivation and the formation of adducts with biological macromolecules has been proposed:	



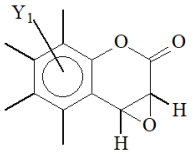
Set of chemicals used for profile development	Pyrrolizidine Derivatives
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Fu, Drug Metabol. Rev. **36**(1) (2004), 1 – 55. 2. Robertson, Canc. Res. **42** (1982), 8 – 14. 3. Reed, Carcinog. **9**(8) (1988), 1355 – 1361. 4. Yamanaka, Mutat. Res. **68** (1979), 211 – 216.

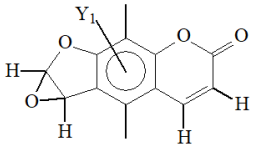
Individual profile/alert	
Name	Aminoacridine DNA Intercalators
Type of profile	Structural alert

Description/applicability domain	 (X can be Cl, Br)  (Y can be H or -NH_2)  (Y_1 can be H or -C(sp3); Y_2 can be -NH_2, -NHC(sp3) or -N(Csp3)2)
Mechanism	**Non-covalent interactions DNA intercalation**
	
Set of chemicals used for profile development	Aminoacridine DNA Intercalators
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Kalinowska, Mutat. Res. **78** (1980), 7 – 15. 2. Yan, J. Med. Chem. **50** (2007), 4096 – 4104. 3. Wainwright, J. Antimicr. Chemother. **47** (2001), 1 – 13. 4. Hoffmann, Chem. Res. Toxicol. **10**(4) (1997), 347 – 359. 5. Fukui, Nucl. Acids Res. **24**(20) (1996), 3962 – 3967. 6. Asseline, Biocon. Chem. **7** (1996), 369 – 379. 7. Huang, Drug Metabol. Dispos. **34**(7) (2006), 1136 – 1144. 8. Denny, Mutat. Res. **232** (1990), 233 – 241. 9. Ferguson, Eur. J. Canc. **26**(6) (1990), 700 – 714.

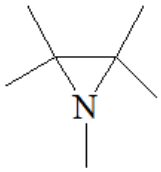
Individual profile/alert	
Name	Epoxides and Aziridines
Type of profile	Structural alert
Description/applicability domain	  (n = 2 - 6)  (m = 1 - 3; n = 1 - 3) (If (CH_2) is acyclic, the terminal group is $-CH_3$; CH_2 can be also cyclic)  (X is Cl or Br or CCl_3 or CBr_3)  Y_1 and Y_2 can be the following structural moeties: (a) $(-CH_2)_nH$ (n = 1 - 2) (b) CH_2{scy} and -CH{scy}=CH{scy}- (c) -CH{sp3}{scy} and O{scy} or -NH{scy} (d) Y_1 is Cl or Br; Y_2 is C  (Y can be Cl, Br or -CHO)  (R is C or N or both)

Laboratory of Mathematical Chemistry
LMC oasis

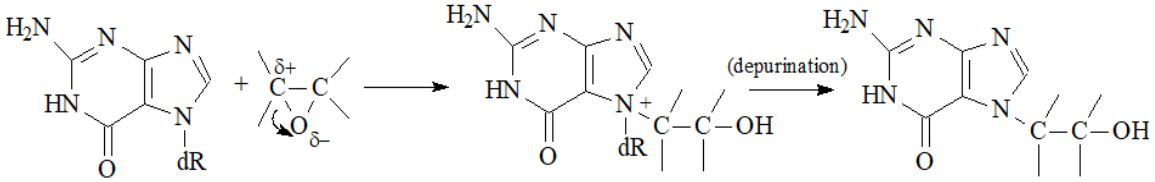




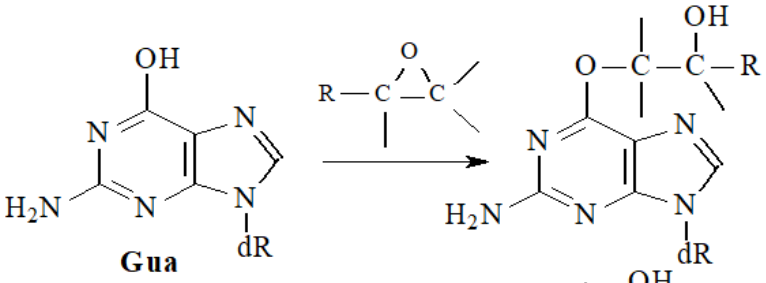
(Y_1 is –H (all) or combinations of H and –OCH_3, -NH_2, -NO_2, -NHOH, -CH_3, -CH_2X (X is Cl, Br); no more than one substituent



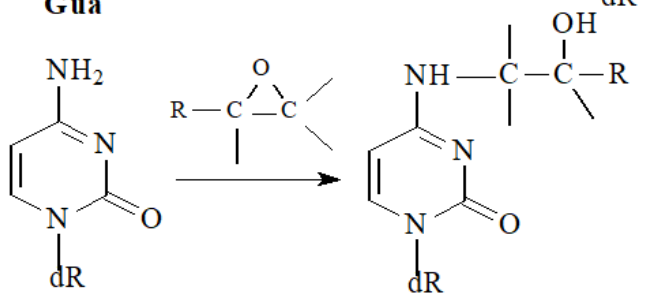
Mechanism	**S_N2 Alkylation, direct acting epoxides and related**



(DNA fragment)
(dR - deoxyribose phosphate fragment)

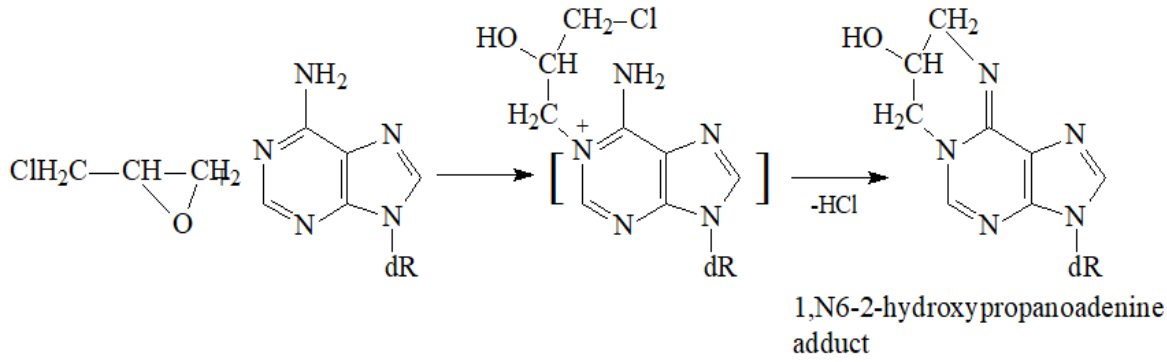


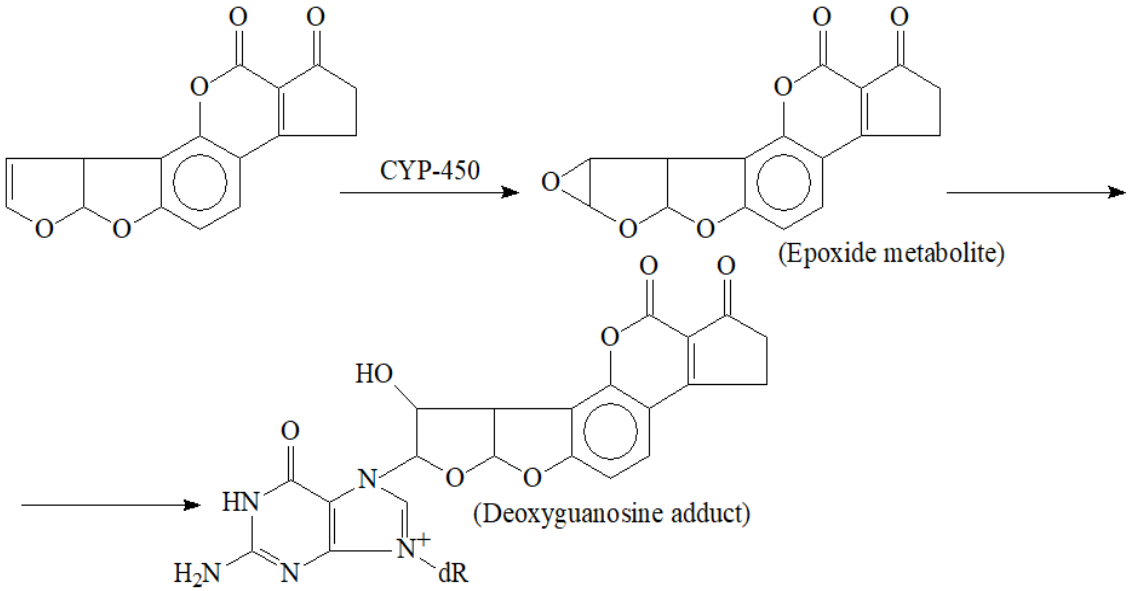
Gua

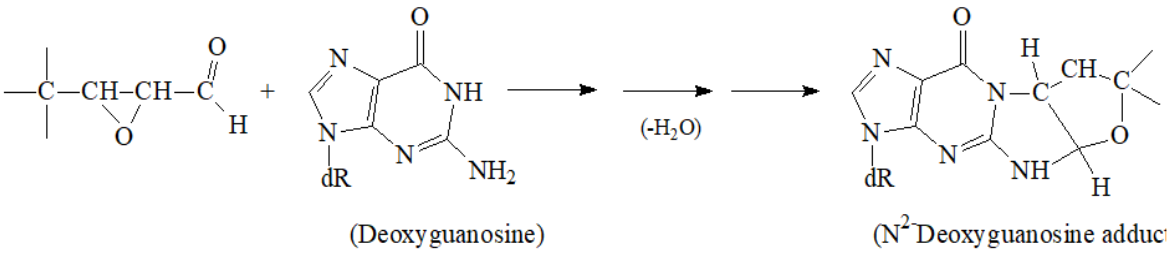


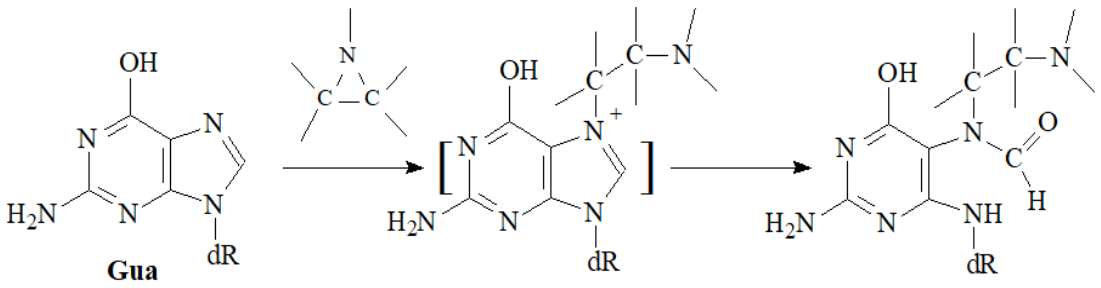
Cyt

(dR - deoxyribose phosphate fragment)


ClH2C—CH—CH2
O
NH2
N
N
N
dR
HO
CH2–Cl
CH
NH2
H2C
+
N
-HCl
CH2
1,N6-2-hydroxypropanoadenine adduct

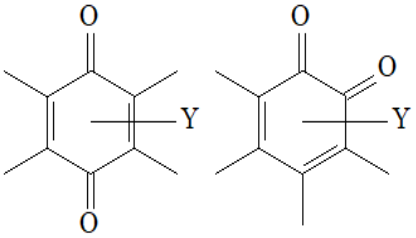
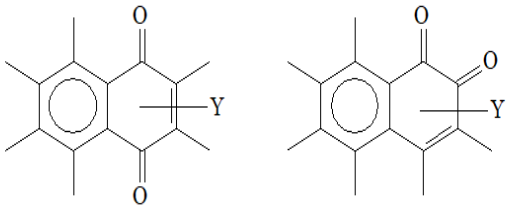
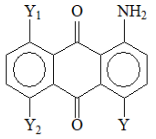
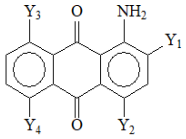
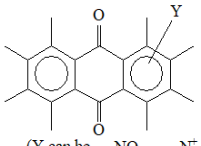
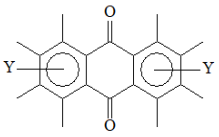

O
O
O
O
CYP-450
(Epoxide metabolite)
HO
HN
H2N
N+
dR
(Deoxyguanosine adduct)

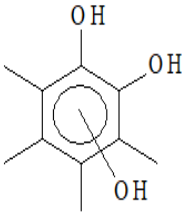
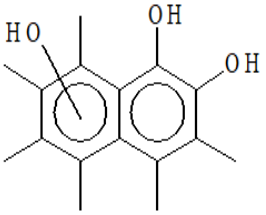

C—CH—CH—C
O
H
+
NH
NH2
dR
(-H2O)
CH
(Deoxyguanosine)
(N2-Deoxyguanosine adduct


OH
N
H2N
dR
Gua
C—C
C—N
+
O
H
NH
(dR - deoxyribose phosphate fragment)
Guanosine ring-opened formamidopyrimidine addu

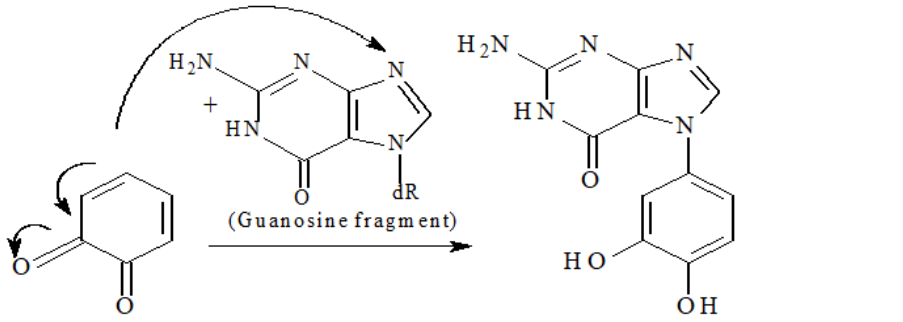
Set of chemicals used for profile development	Epoxides and Aziridines
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Koskinen, M., Chem.-Biol. Interact. **129** (2000), 209 – 229. 2. Singh, U. S., Chem. Biol. Interact. **99** (1996), 109 – 128. 3. Sawatari, K., Industrial Health **39** (2001), 341 – 345. 4. Raney, V. M., Chem. Res. Toxicol. **6** (1993), 64 – 68. 5. Wade, M. J., Mutat. Res. **66** (1979), 367 – 371. 6. Voogd, C. E., Mutat. Res. **89** (1981), 269 – 282. 7. Hemminki, K., Arch. Toxicol. **46** (1980), 277 – 285. 8. Von der Hude, Mutat. Res. **231** (1990), 205 – 218. 9. Frantz, S. W., Mutat. Res. **90** (1981), 67 – 78. 10. Meester, C. De, Toxicol. Lett. **224** (1984), 255 – 262. 11. Sinsheimer, J. E., Mutat. Res. **224** (1989), 171 – 175. 12. Glatt, H., Mutat. Res. **11** (1983), 99 – 118. 13. *Vinylidene Chloride*, Chemical Carcinogenesis Research Informartion System (CCRIS), US National Library of Medicine; http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?CCRIS. 14. Neudecker, T., Biochem. Pharmacol. **35**(2) (1986), 195 – 200. 15. Petrova, K. V., Chem. Res. Toxicol. **20** (2007), 1685 – 1692. 16. *Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contacts with Food (AFC) on a Request from the Commission Related to Coumarin*, Question Number EFSA-Q-2003-118 (6 October 2004), The EFSA Journal **104** (2004), 1 – 36; DOI: 10.2903/j.efsa.2004.104. 17. Born, S. D., Drug Metab. Dispos. **30**(5) (2002), 483 – 487 18. Zhou, S., Life Sci **74** (2004), 935 – 968. 19. Cussac, C., Nucleic Acids Res. **24**(9) (1996), 1742 -1746. 20. Tudek, B., J. Biochem. Molec. Biol. **36**(1) (2003), 12 – 19. 21. Glatt, H., Canc. Res. **45** (1985), 2600 – 2607. 22. *Divinylbenzene, CAS No. 1321-74-0*, Chemical Carcinogenesis Research Information System; http://toxnet.nlm.nih.gov/cgi-bin/sis/search/r?dbs+ccris:@term+@rn+1321-74-0

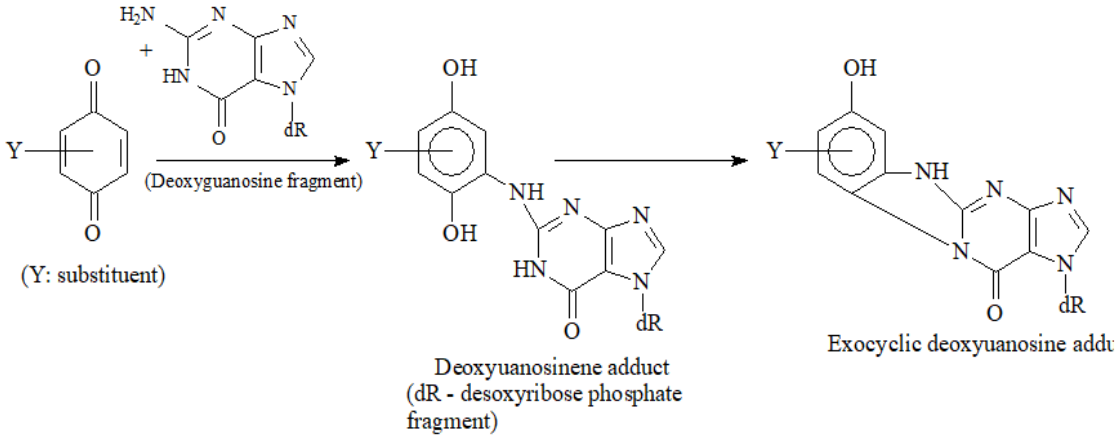
Individual profile/alert	
Name	Quinones and Trihydroxybenzenes
Type of profile	Structural alert

Description/applicability domain	 (Y can be Cl, Br (more than one); -CN, -NO_2, -C=O, -CHOH or H or C{ar}or N{acy}{V3}or -$CH(CH_3)_2$ or -$C(CH_3)_3$ or combinations with -H), -CH_2-NH- no other substituents; for catechol quinones Y = -OH should be added  1,4-Naphthoquinones 1,2-Naphthoquinones Y can be any combination of substituents such as –H, -CH_3, -OH, -OCH_3, -NH_2, -$NHCH_3$, –Cl, -Br, -CN, -CX_3 (X = Cl, Br), -$C(O)CH_3$, -$C(O)OCH_3$; Y can be attached to one or to both rings; No more than totally two fused rings in the molecular structure  (Y can be -OH or -NH; Y_1, Y_2 can be -OH, -NH_2 or -H)  (Y_1 can be -Cl, -Br, -COOH, -OH, -OCH_2 or -NH_2); Y_2 can be Cl or Br or -H; Y_3, Y_4 can be -OH, -NH_2 or -H)  (Y can be —NO_2 —$N^+{\equiv}N$ —N=NH N{V_3}—N{V_3}; could be anywhere)  (Y is -OH or -CH_2OH or -H or -O-C{sp3} or -C(C{sp3})$_3$ or C{scy}{sp3} or -$NHCH_3$ or -$NHCH_2$OH or -NHC_2H_5 or -$NHCH_2CH_2$OH or -NH-C(O)-C_6H_5 or combinations)

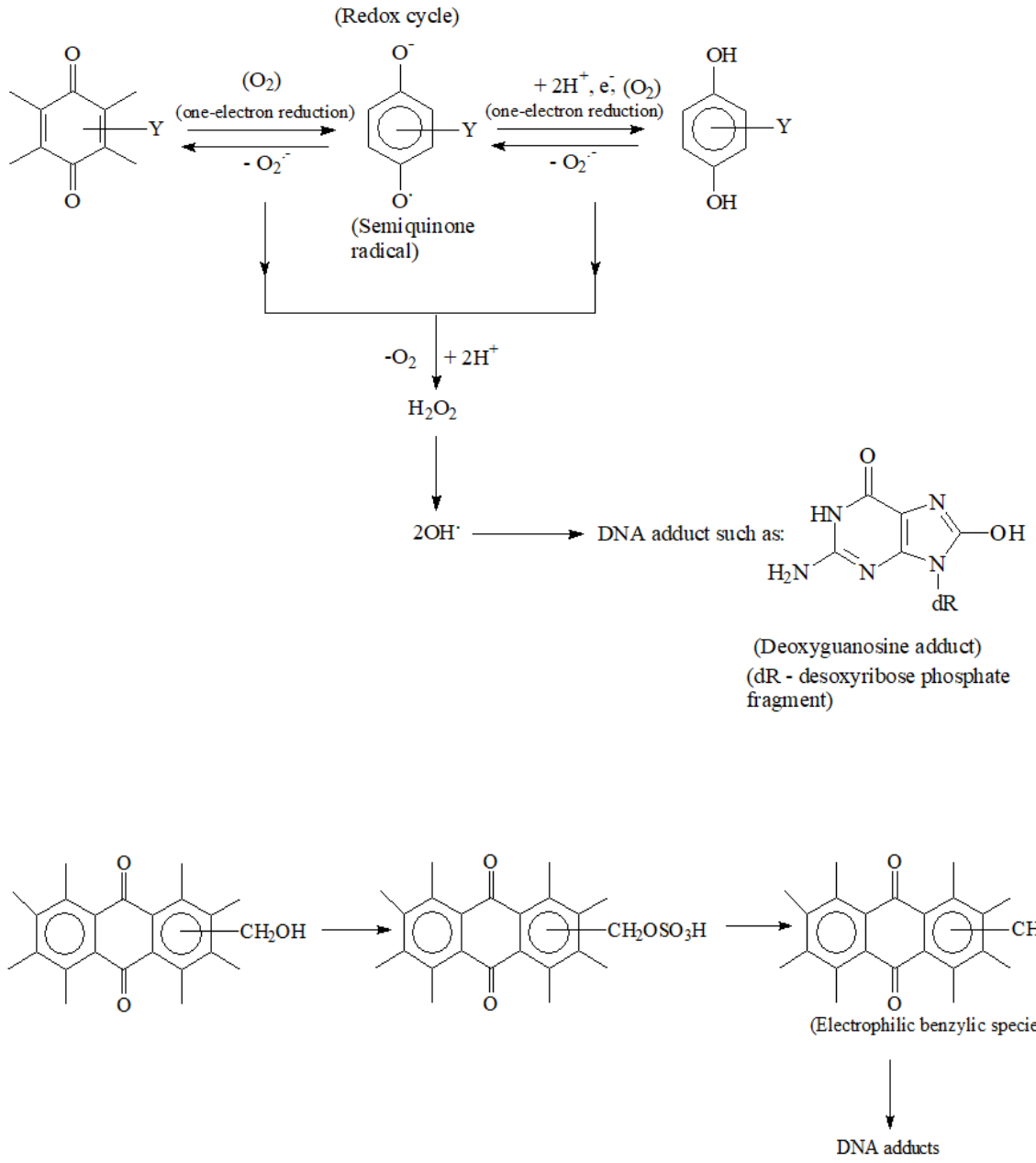
	  (Other possible substituents: -H, $-CH_3$,$-OCH_3$, $-NH_2$; No substituents other than these)
Mechanism	**A_N2 Michael-type addition, quinoid structures , Radical ROS generation (indirect) & Non-covalent interactions DNA intercalation**

1. Electrophilic mechanism for simple quinones and naphthoquinones:





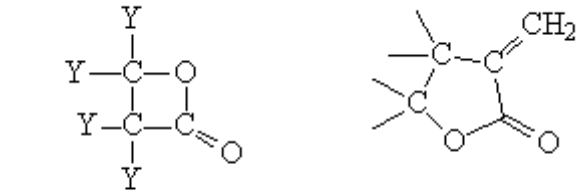
2. Radical mechanism for simple quinones, naphthoquinones, anthraquinone derivatives and trihydroxybenzenes



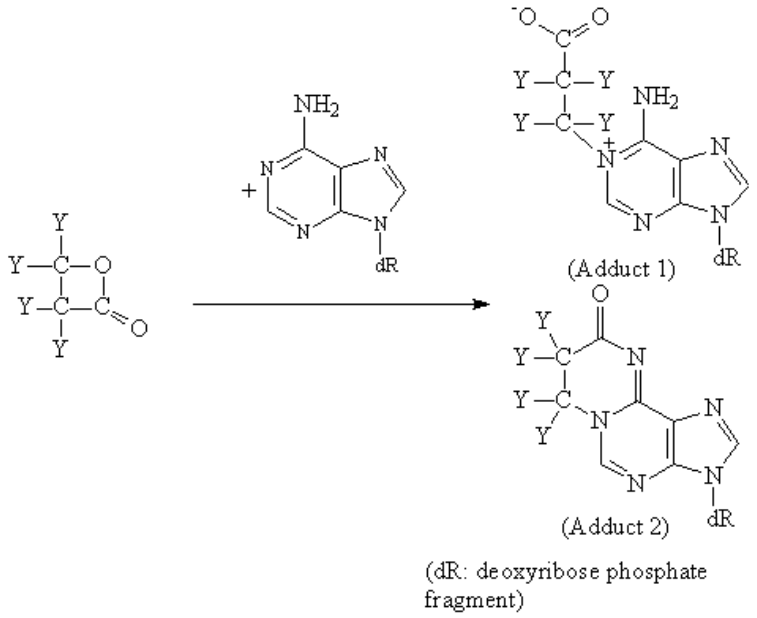
Set of chemicals used for profile development	Quinones and Trihydroxybenzenes
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Hakura, A., Mutat. Res. **347** (1995), 37 – 43). 2. Nagabhushan, M., *Environ. Mutagen.* 7(6) (1985**)**, 881 – 888. 3. Chanda, S., Drug Metab. Dispos. **36** (2008), 670 -675. 4. Reilly, Chr., Chem. Res. Toxicol. **16** (2003), 336 – 349. 5. Watanabe, K., *Mutat. Res.* 412(1) (1998**)**, 17 - 31). 6. Gocke, E., Mutat. Res. **90**(2) (1981), 91 – 109. 7. Ben-Gurion, R., Mutat. Res. **68**(3) (1979), 201 – 205. 8. Takemura, Y., Bull. Environ. Contam. Toxicol. **84**(3) (2010), 347 - 350. 9. Opinion on 1,2,4-Trihydroxybenzene, COLIPA No. A33,

	Scientific Committee on Consumer Safety SCCS 11 December **2012**; http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_113.pdf 10. Lin, J.K., Mutat. Res. **269**(2) (1992), 217 – 224. 11. Tourino, S., EJEAFChe 7(8) (2008), 3348 – 3352. 12. Hakura, A., Chem. Res. Toxicol. **7** (1994), 559 – 567. 13. DaCosta, Mutat. Res. **650** (2008), 140 – 149. 14. Cavalieri, E., Carcinog. **23**(6) (2002), 1071 – 1077. 15. Hakura, A., Chem. Res. Toxicol. **7** (1994), 559 – 567. 16. Tikkanen, L., Mutat. Res. **124** (1983), 25 – 34. 17. *Opinion Proposing Harmonized Classification and Labelling at Community Level of Acequinocyl*, ECHA/RAC/CLH-O-0000001401-89-01/F, Committee for Risk Assessment RAC, Adopted 28 October 2010; https://echa.europa.eu/documents/10162/de28d339-f99c-e6d7-564a-35a66a4319bc, last visited 10.2019. 18. Brown, J. P., Mutat. Res. **66** (1979), 9 – 24. 19. Bosch, R., Mutat. Res. **188** (1987), 161 – 168. 20. Poginsky, B., Carcinogenesis **12**(7) (1991), 1265 – 1271. 21. Westendorf, J., Cell Biol. Toxicol. **4**(2) (1988), 225 – 229. 22. Marzin, D., Eur. J. Cancer Clin. Oncol. 19(5) (1983), 641 – 647. 23. CCRIS: Daunomycin CASRN 20830-81-3, Toxicology Data Network, U.S. National Library of Medicine**;** http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+ccris:@term+@rn+20830-81-3); 24. Benedict, W.F., Cancer Res. **37**(7) Pt 1 (1977) 2209 – 2213. 25. Bachur, N. R., Br. J. Pharmac. **43** (1971), 828 – 833. 26. CCRIS: Doxorubicin CASRN 23214-92-8, Toxicology Data Network, U.S. National Library of Medicine**;** http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+ccris:@term+@rn+23214-92-8. 27. Bhuyan, B.K., Cancer Res. **43**(11) (**1**983**)**, 5293 - 5297. 28. Kalgutkar, A. S., Current Drug Metabol. **6** (2005), 161 – 225. 29. Gaskell, M., Carcinogenesis **26**(3) (2005), 673 – 680. 30. Park, J. Z., Carcinogenesis **25**(9) (2004), 1727 – 1733. 31. Li, K. M., Carcinogeneis **25**(2) (2004), 289 – 297. 32. Singh, M. W., A. Karmakar, N. Barooah, J. B. Baruah, *Variation in Product in reactions of Naphthoquinone with Primary Amines*, Beil. J. Org. Chem. **3**(10) (2007), 1 – 6. 33. Gaskell, M., Chem. Res. Toxicol. **15** (2002), 1088 – 1095. 34. Xie, Zh., DNA Repair **4** (2005), 1399 – 1409. 35. Yu, D., Chem. Res. Toxicol. **15** (2002), 832 – 842. 36. Kovacic, P., Current Med. Chem. **8** (2001), 773 – 796. 37. Gouda, M. A., Turk. J. Chem. **34** (2010), 651 – 709. 38. Poginsky, B., Carcinogenesis **12**(7) (1991), 1265 – 1271. 39. Double, J. C., J. Pharm. Pharmac. **28** (1976), 166 – 169. 40. Brock, K. H., Mutagen. **6**(1) (1991), 35 – 46.

Individual profile/alert

Name	Four- and Five- membered Lactones
Type of profile	Structural alert
Description/applicability domain	 (Y can be -H and/or $-CH_3$, C_2H_5)
Mechanism	**Ring opening S_N2 reaction (alkylation) and A_N2 Michael-type addition on α,β-unsaturated carbonyl compounds**

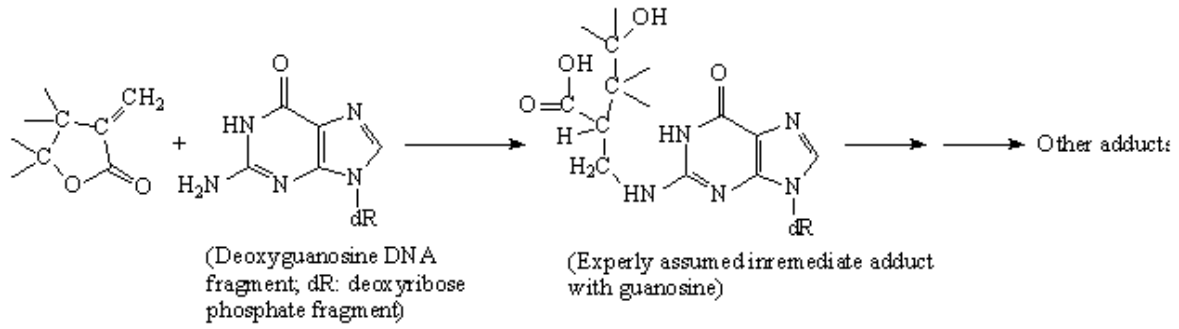
The following mechanistic Scheme 1 for the DNA adducts formation at the N1 site of adenosine nucleotide elicited by four-membered lactones of high reactivity can be outlined based on literature:



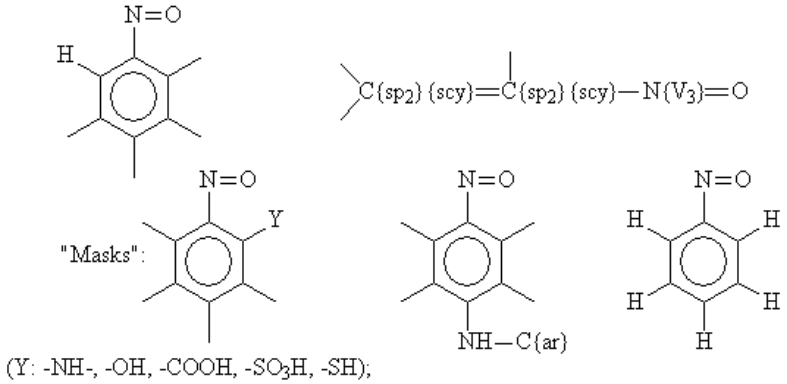
(dR: deoxyribose phosphate fragment)

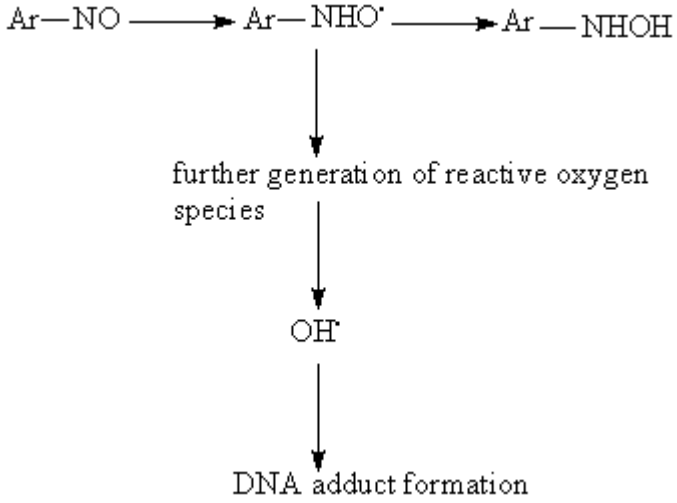
Scheme 1

The conjugated system in the molecular structure of some alpha-methylidene-γ-butyrolactone derivatives might actually cause bacterial mutagenicity by expertly assumed (hypothetic) mechanistic Scheme 2, similar to that for some α,β-unsaturated systems:



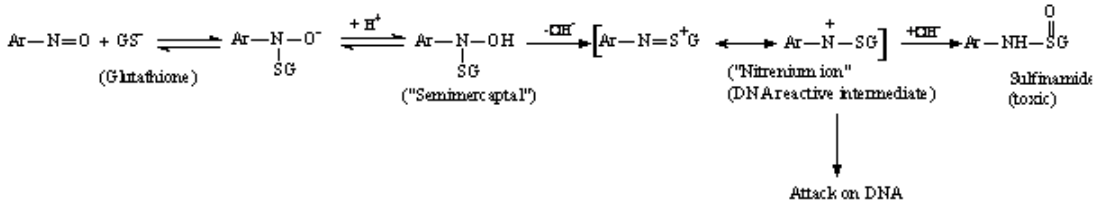
Set of chemicals used for profile development	Four- and Five-Membered Lactones
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Hemminki, Chem. Biol. Interact. **34** (3), 1981, 323 - 331. 2. Beta-Butyrolactone (CAS 3068-88-0), The Carcinogenic Potency Project; http://potency.berkeley.edu/chempages/beta-BUTYROLACTONE.html 3. Sawatari, Industrial Health **39**, 343 (2001), 341 – 345. 4. Chen, Carcinog. **2**(2) (1981), 73 – 80. 5. Kupchan, J. Med. Chem. **14**(12) (1971), 1147 – 1152. 6. Picman, Biochem. System. Ecol. **14**(3) (1986), 255 – 281.

Individual profile/alert	
Name	C-Nitroso Compounds
Type of profile	Structural alert
Description/applicability domain	
Mechanism	**S_N1 Nucleophilic substitution after glutathione-induced nitrenium ion formation and Radical ROS generation (indirect)**
Radical mechanism - the formation of reactive entities such as $ArNHO^{\cdot}$ is known to be implicated in the oxidative DNA damage. Nitrosoarene functionality has superior ability in electron uptake and, for example, nitrosopyrene *in vivo* has significant contribution to the DNA adduct formation. The following mechanistic Scheme 1 is assumed to operate in such cases [6]:	



Scheme 1

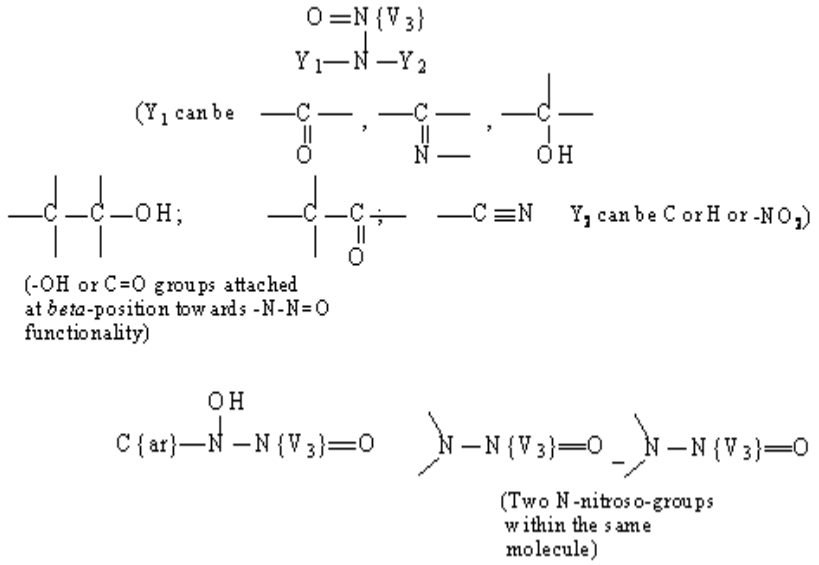
-Non-Radical Mechanism: pseudo-nitrenium ion formation with glutathione (or other thiols) Scheme 2 [4]:



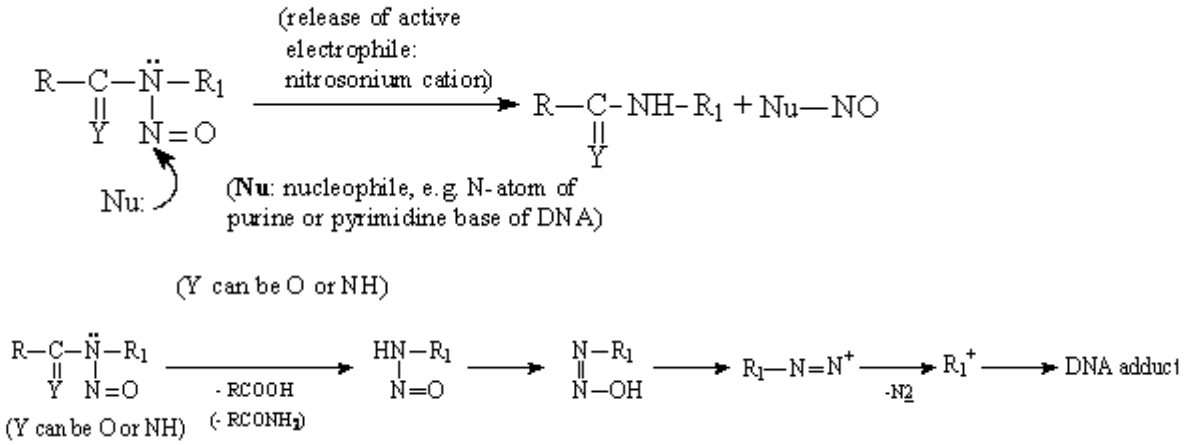
Scheme 2

Set of chemicals used for profile development	C-Nitroso Compounds
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. McCoy, Mutat. Res. **173** (1986), 245 – 250. 2. *Chemical Carcinogenesis Research Information System (CCRIS)*; http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?CCRIS. 3. Kranendonk, Mutag. **12**(4) (1997), 245 – 254. 4. Eyer, Environ. Health Persp. **102**, Suppl. 6 (1994), 123 – 132. 5. Galleman, Environ. Health Persp. **102** (Suppl. 6) (1994), 137 – 142. 6. Kovacic, PCurrent Med. Chem. **8** (2001), 773 – 796. 7. Witherell, Canc. Epidemiol. Biomarkers & Prevention **7** (1998), 91 – 96. 8. Wiseman, Biochem. J. **313** (1996), 17 – 29.

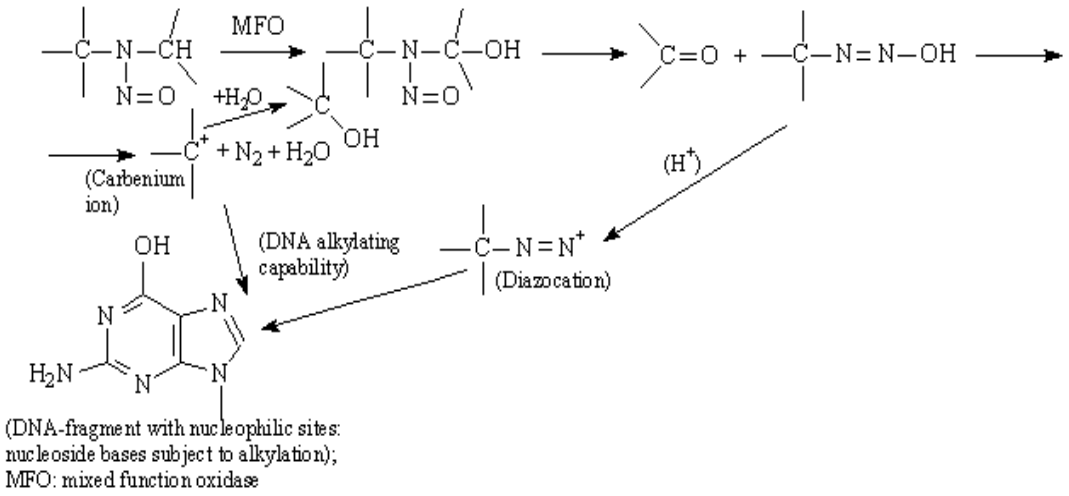
Individual profile/alert	
Name	N-Nitroso Compounds
Type of profile	Structural alert

Description/applicability domain	
Mechanism	**S_N1 Nucleophilic attack after carbenium ion formation & S_N1 Nucleophilic attack after nitrosonium cation formation**

1. Mutagenicity without metabolic activation.

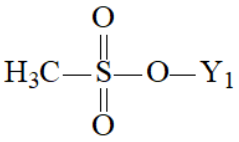
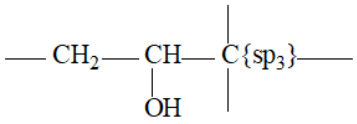
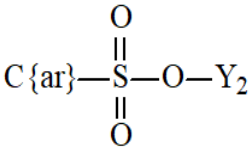
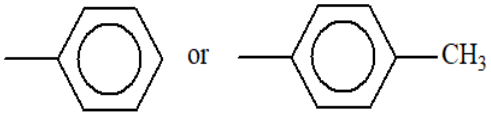


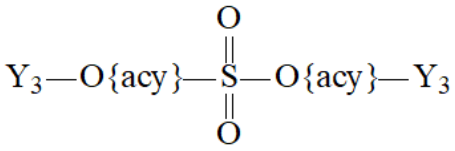
2. Mutagenicity with metabolic activation.



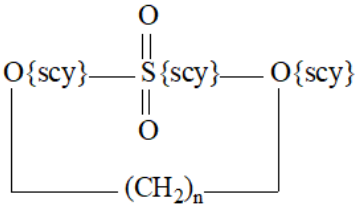
Set of chemicals used for profile development	N-Nitroso Compounds
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. *Toxicological Profile for N-Nitrosodiphenylamine*, US Dept. of Health and Human Services, Public Health Service, Agency for Toxic Substances and Sisease Registry, April 1993; http://www.atsdr.cdc.gov/ToxProfiles/tp16.pdf 2. Miura, M., Tetrahedron Lett. **41** (2000), 3637 – 3641. 3. Kovacic, P., Current Med. Chem. **8**, (2001), 773 – 796. 4. Wang, P. G., Chem. Rev. **102** (2002), 1091 – 1134. 5. Janczuk, *Nitric Oxide Donors: Chemical Activities and Biological Applications*, Chem. Rev. **102** (2002), 1091 – 1134. 6. Guttenplan, J. B., Mutat. Res. **186** (1987), 81 – 134. 7. Ethylnitrosocyanamide CASRN: 38434-77-4, GENE-TOX, Toxicology Data Network, U.S. National Library of Medicine; http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+genetox:@term+@rn+@rel+38434-77-4). 8. Nakamura, S.-i., Mutat. Res. **192** (1987), 239 – 246. 9. Lee, K., Mutat. Res. **48** (1977), 131 – 138. 10. *Chemical Carcinogenesis Research Information System (CCRIS)*; http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?CCRIS (for bacterial mutagenicity data for chemicals such as Dinitrosopentamethylenetetramine, N-nitroso phenylhydroxylamine and N-Nitrosodiethanolamine. 11. Kushida, H., Carcinogenesis **21**(6) (2000), 1227 – 1232. 12. Maertens, L. A., Drug Metabol. Dispos. **38** (2010), 752 – 760. 13. Peterson, L. A., Canc. Res. **61** (2001), 5757 – 5763. 14. *N-Nitrosomethylethylamine, Summaries & Evaluations*, IARC, Vol. 17 (1978), p. 221; http://www.inchem.org/documents/iarc/vol17/nitrosomethylethylamine.html. 15. Farelly, J. G., Canc. Res. **42** (1982), 2106 – 2109. 16. Von Hofe, E., Canc. Res. **46** (1986), 1038 – 1042. 17. Rao, T.K., Mutat. Res. 89(1) (1981**)**, 35 – 43. 18. Rao, T.K., Mutat. Res**. 67**(1) (1979), 21 - 26.

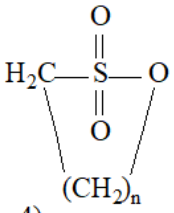
	19. Padma, P.R., Cancer Lett. **46**(3) (1989), 173 - 180. 20. N-Nitroso-1,2,3,6-Tetrahydropyridine CASRN: 55556-92-8, GENE-TOX, Toxicology Data Network, U.S. National Library of Medicine; http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+genetox:@term+@rn+@rel+55556-92-8.

Individual profile/alert	
Name	Sulfonates and Sulfates
Type of profile	Structural alert
Description/applicability domain	 (Y_1 is $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$ $-CH_2CH_2CH_3$, $-CH(CH_3)CH_2CH_3$ $-(CH_2)_n$-O-S{V6}, n = 1 - 4), $-CH_2CH_2CH(CH_3)_2$   (Y_2 is $-CH_3$, $-CH_2CH_3$ $-CH(CH_3)_2$, $-CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$ $-CH_2CH_2Y$ (Y is Cl, Br, O, N, C{ar})) C{ar} is carbon atom in benzenoid aromatic nucleus such as : 



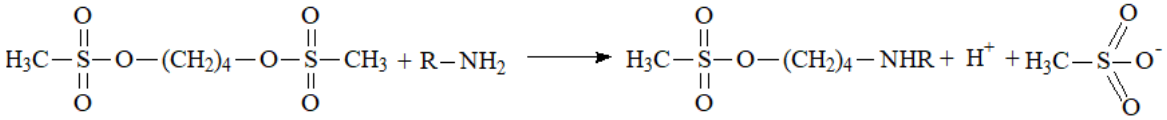
(Y_3 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$ or combinations)



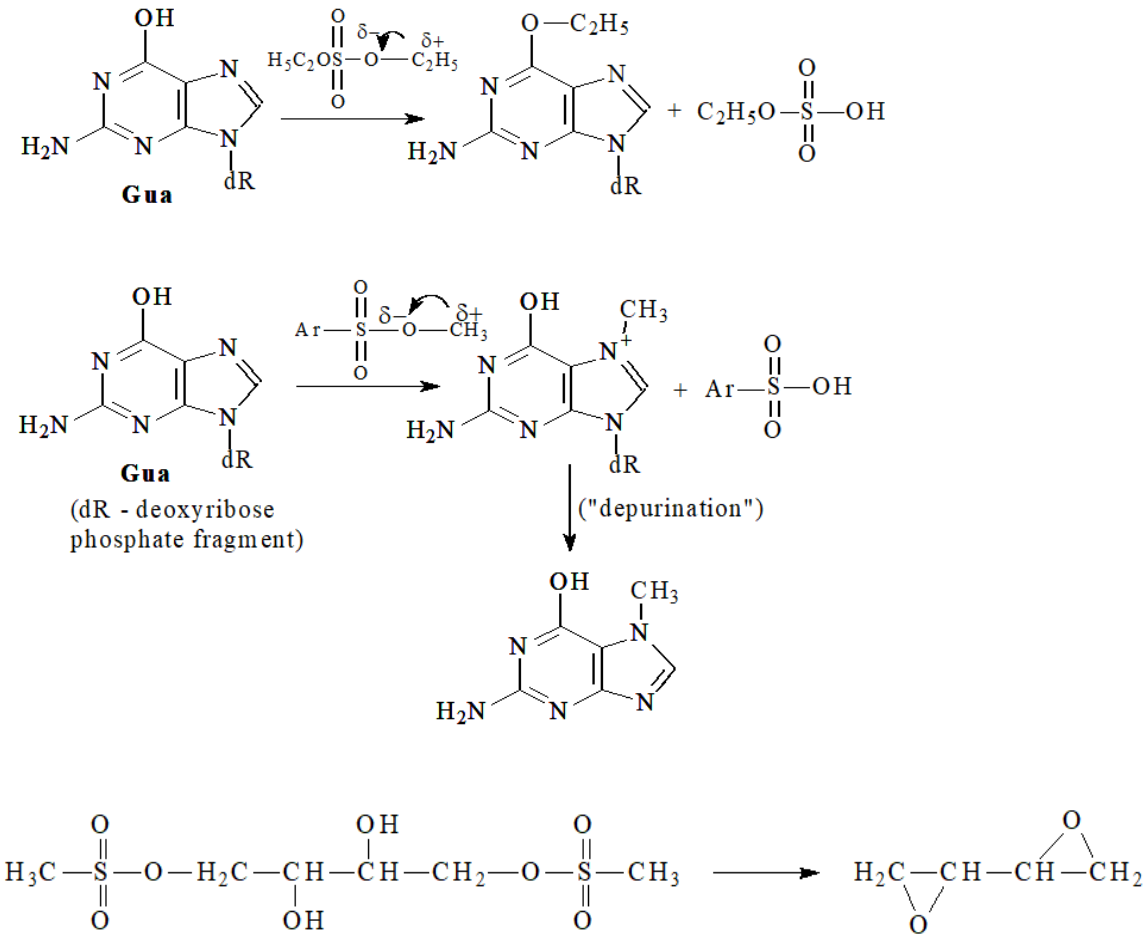


(n = 2 - 4)

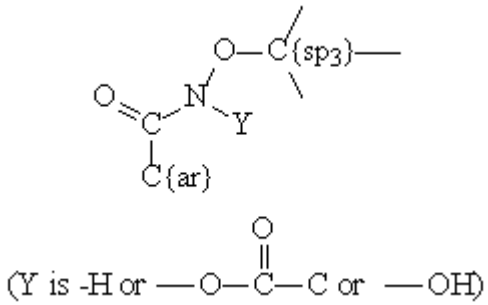
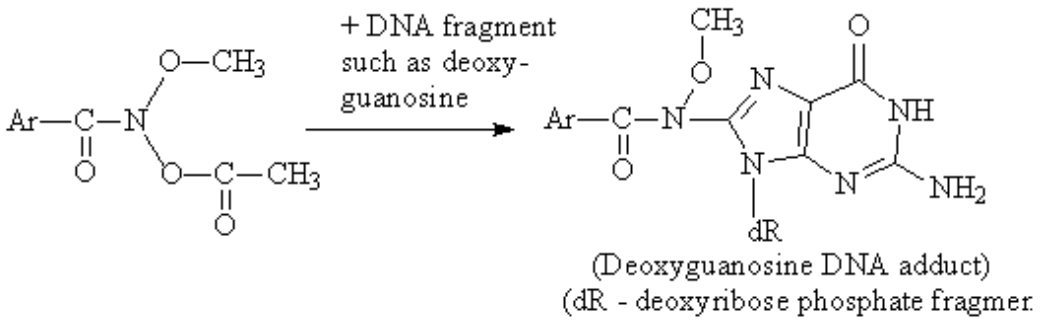
Mechanism	**S_N2 at sp3-carbon atom (alkylation)**

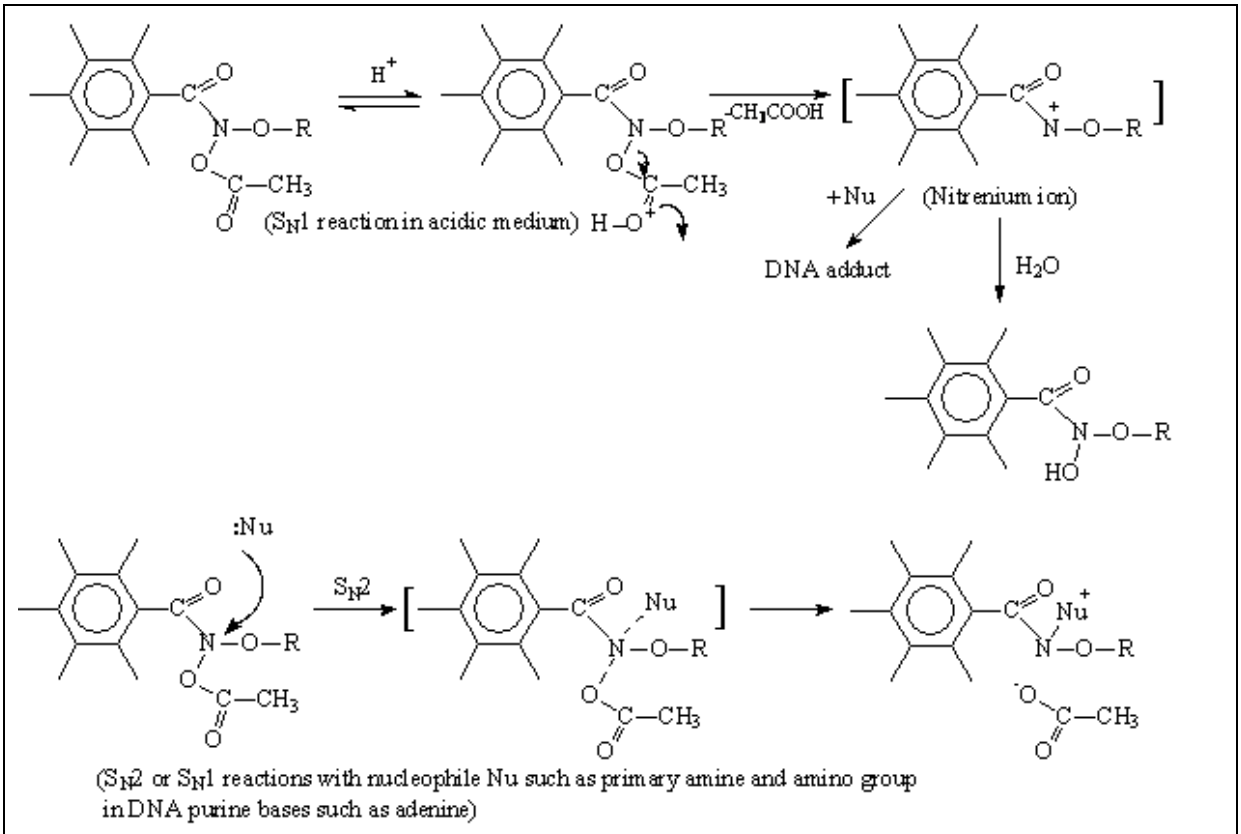


($R\text{-}NH_2$: biological macromolecule (e.g., adenine or guanine fragment in DNA)



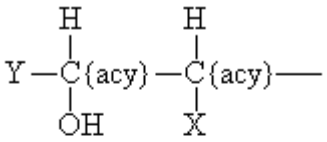
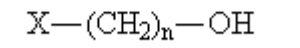
Set of chemicals used for profile development	Sulfonates and Sulfates
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Colvin, M., *Alkylating Agents and Platinum Antitumor Compounds* (In Ch. 51, Section 12: Chemotherapeutic Agents, Holland-Frei Cancer Medicine, 6th Ed., Kufe DW, Pollock RE, Weichselbaum RR, et al. (Editors), Hamilton (ON): BC Decker; 2003; http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=cmed6.figgrp.12445. 2. Kovacic, P., Current Med. Chem. **8**, (2001), 773 – 796. 3. Couch, D. B., Mutat. Res. **57**(2) (1978), 217 - 224. 4. Sanderson, B. J. S., Mutat. Res. **355** (1996), 41 – 57. 5. Kazius, J., J. Med. Chem. **48** (2005), 312 – 320. 6. Hopppe, H., Canc. Res. **38** (1978), 1595 – 1600. 7. McCann, J., Proc. Nat. Acad. Sci. USA **72**(12) (1975), 5135 – 5139. 8. Abu-Shakra, A., Mutat. Res. **470**(1) (2000), 11 – 18. 9. Zeiger, E., Environ. Mol. Mutagen. **13**(4) (1989), 343 – 346. 10. Hartley, J. A., Brit. J. of Cancer **79**(2) (1999), 264 – 266.

Individual profile/alert	
Name	N-Acyloxy(Alkoxy) Arenamides
Type of profile	Structural alert
Description/applicability domain	 (Y is -H or —O—C—C or —OH)
Mechanism	**S_N2 or S_N1 reaction at nitrogen-atom bound to a good leaving group or on nitrenium ion**
 (Deoxyguanosine DNA adduct) (dR - deoxyribose phosphate fragmer	

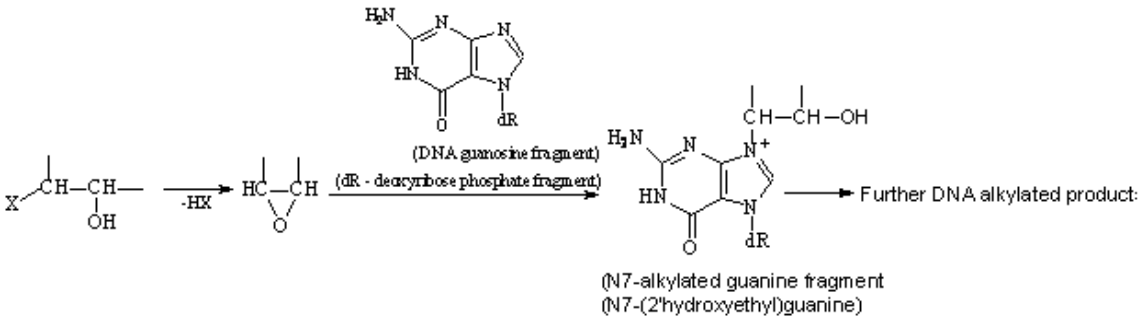


Set of chemicals used for profile development	N-Acyloxy(Alkoxy) Arenamides
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1.Glatt, Carcinogenesis **25**(5) (2004), 779 – 786. 2. Banks, Org. Biomolec. Chem. **1**(13) (2003), 2238 – 2246. 3. Bonin, Mutat. Res. **494** (2001), 115 – 134.

Individual profile/alert	
Name	Haloalcohols
Type of profile	Structural alert

Description/applicability domain	 (Y can be C(sp3) or -H) (X = Cl, Br, J)  (X is Cl, Br, n = 3 - 10)
Mechanism	**S_N2 Alkylation, direct-acting epoxide formed after E2 reaction and Radical ROS formation after GSH depletion (indirect)**

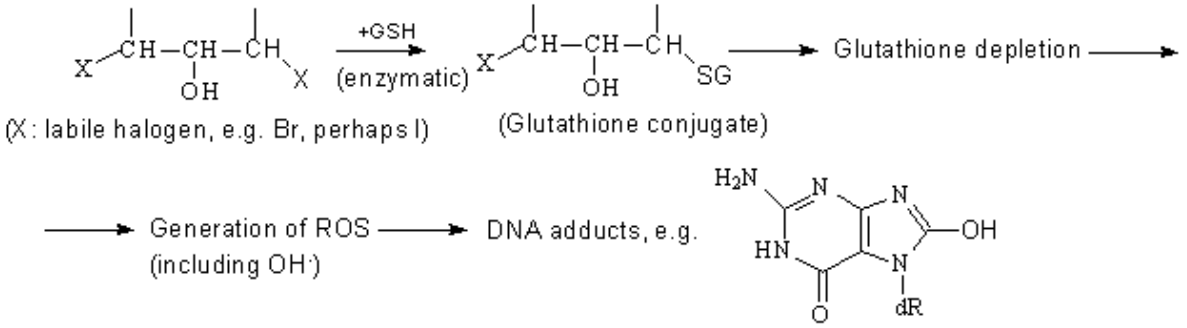
The metabolism of 1,3-dichloropropan-2-ol is likely to produce a reactive epoxide intermediate that could damage DNA, and this compound was found to be mutagenic to *Salmonella typhimurium* strains TA1535 and/or TA 100. 2,3 Dichloropropan-1-ol, on the other hand, was also mutagenic *in vitro* in *Salmonella typhimurium* strains TA 100 and TA 1535 in a study with and without metabolic activation [1]. The formation of epoxide intermediate (mutagenicity alert group) can be influenced by *haloalcohol dehalogenases* which are bacterial enzymes that catalyze the cofactor-independent dehalogenation of vicinal haloalcohols. Typical example in this respect is again the genotoxic environmental pollutant 1,3-dichloro-2-propanol, which produces epoxide, chloride ion and proton [2]. Then the epoxide is likely to exert its DNA alkylation capability shown in Scheme 1 [3]:



Scheme 1

Some authors have assumed genotoxicity mechanism, associated with glutathione depletion as glutathione S-transferase was used as the enzyme source, especially with bromohydrins such as 1,3-dibromopropanol [4]. It is likely that the protection afforded by glutathione against the toxicity of this chemical is mediated through the activity of cytosolic glutathione S-transferase. While 1,3-dichloro-2-propanol is relatively poor substrate for glutathione S-transferase, the dibromo-analogue causes extensive glutathione depletion [4]. According to another study, dichloropropanols such as 1,3-dichloropropan-2-ol, 2,3-dichloropropan-1-ol, 1,3-dibromopropan-2-ol, 1,4-dibromopropan-2-ol, 1-bromopropan-2-ol, other haloalcohols and their metabolites such as epichlorohydrin have been proved to deplete glutathione when incubated with liver fractions obtained from rats. However, difluoropropanols did not deplete glutathione [5].

It is therefore expertly assumed that glutathione depletion would further give rise to formation of ROS and DNA adducts in Scheme 2:



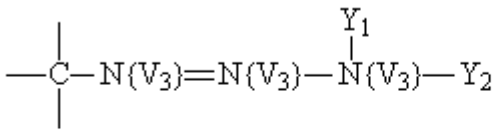
Such mechanistic scheme could also apply to haloalcohols of the type:

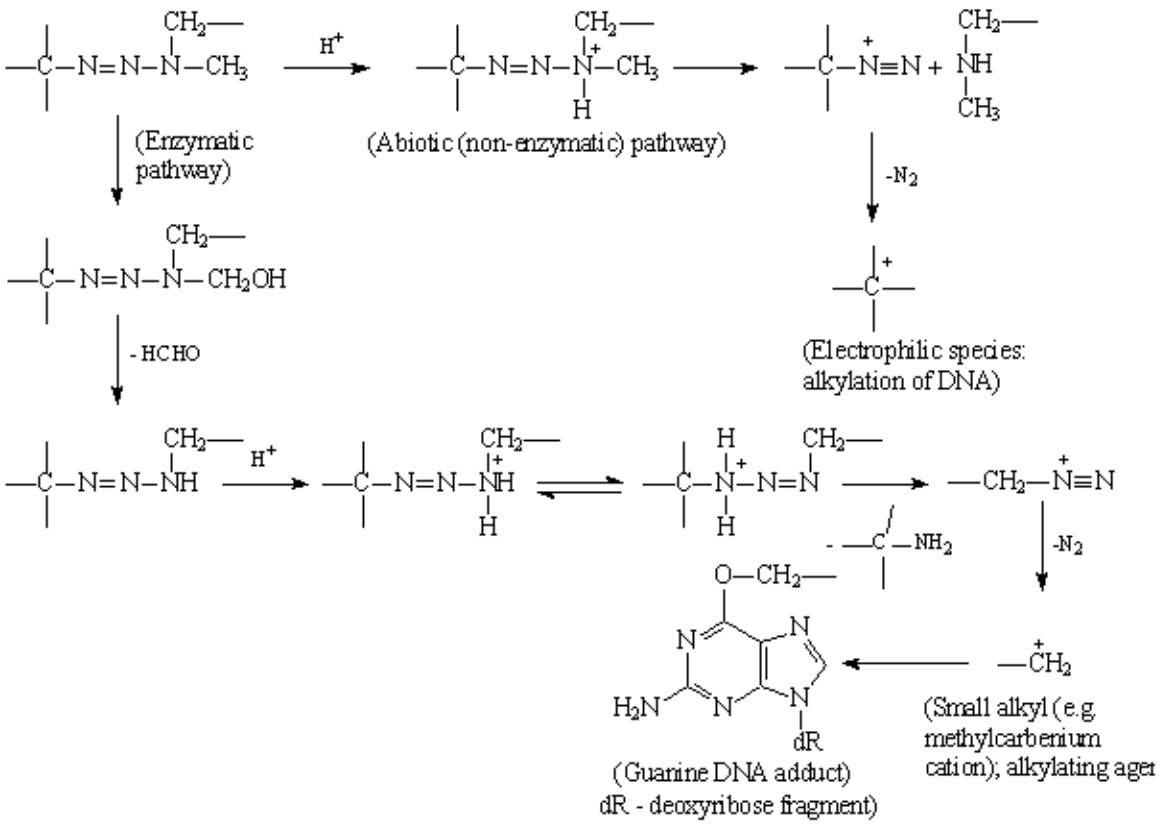
$$X—(CH_2)_n—OH$$

(X is Cl, Br, n = 3 - 10)

Scheme 2

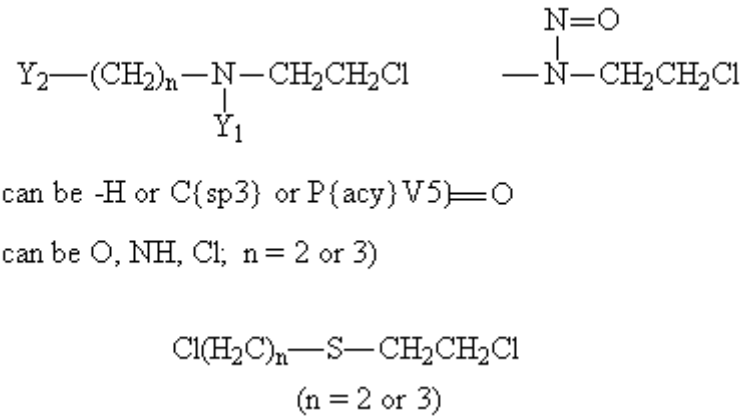
Set of chemicals used for profile development	Haloalcohols
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1.*Carcinogenicity of 1,3-Dichloropropan-2-ol (1,3-DCP) and 2,3-Dichloropropan-1-ol (2,3-DCP)*, Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment, COC/04/S2 – June 2004; http://www.iacoc.org.uk/statements/statement123dichloropropanjune2004.htm 2. De Jong, The EMBO Journal **22**(19) (2003), 4933 – 4944. 3. Saha, J. Chromatogr. A **712** (1995), 345 – 354. 4. Hammond, Toxicol. Appl. Pharmacol. **155**(3), 1999, 287-291. 5. Garle, Xenobiotica **29**(5) (1999), 533 – 545.

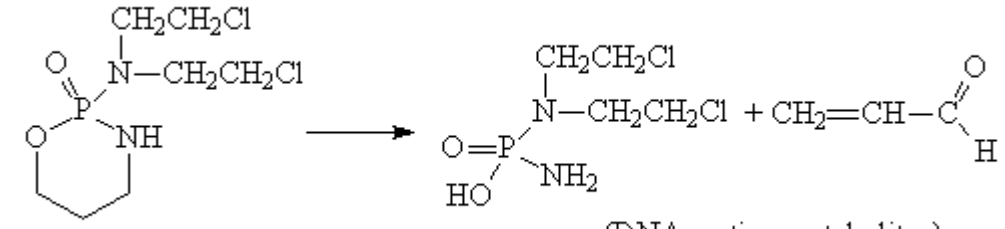
Individual profile/alert	
Name	Acyclic Triazenes
Type of profile	Structural alert
Description/applicability domain	 (Y_1, Y_2 are $-CH_3$, or $-H_2C-C_6H_5$ or $-CH_2CH_3$ or -H or $-CH(CH_3)_2$ (number of -H can be 0 or 1))
Mechanism	**S_N1 Nucleophilic attack after carbenium ion formation**
On the basis of the literature data available, the following scheme of bioactivation of triazene derivatives can be expertly assumed:	

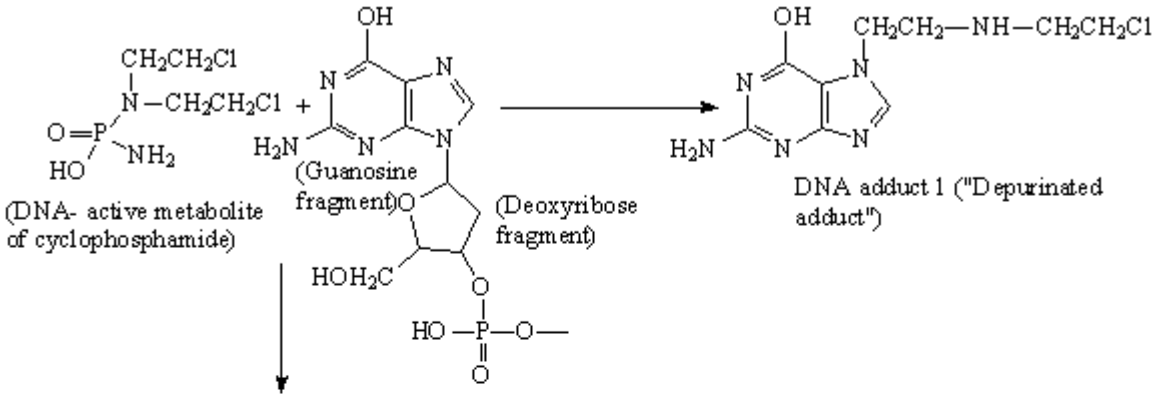


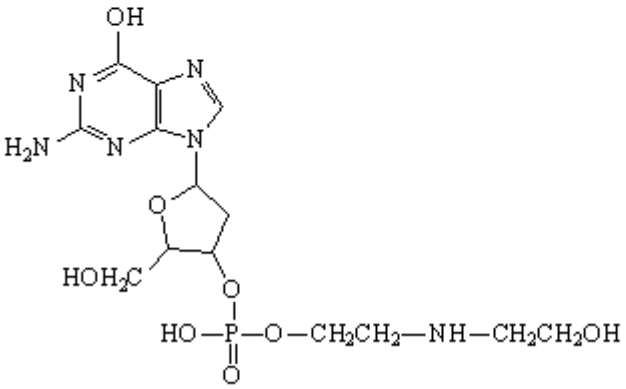
Set of chemicals used for profile development	Acyclic Triazenes
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Kazius, J. Med. Chem. **48** (2005), 312 – 320. 2. Thomas, Mutat. Res. **60** (1979), 25 – 32. 3. Malaveille, Canc. Res. **42** (1982), 1446 – 1453. 4. Marchesi, Pharmacol. Res. **56** (2007), 275 – 287. 5. Sieh, Mutat. Res. **73** (1980), 227 – 235.

Individual profile/alert	
Name	Nitrogen and Sulfur Mustards
Type of profile	Structural alert

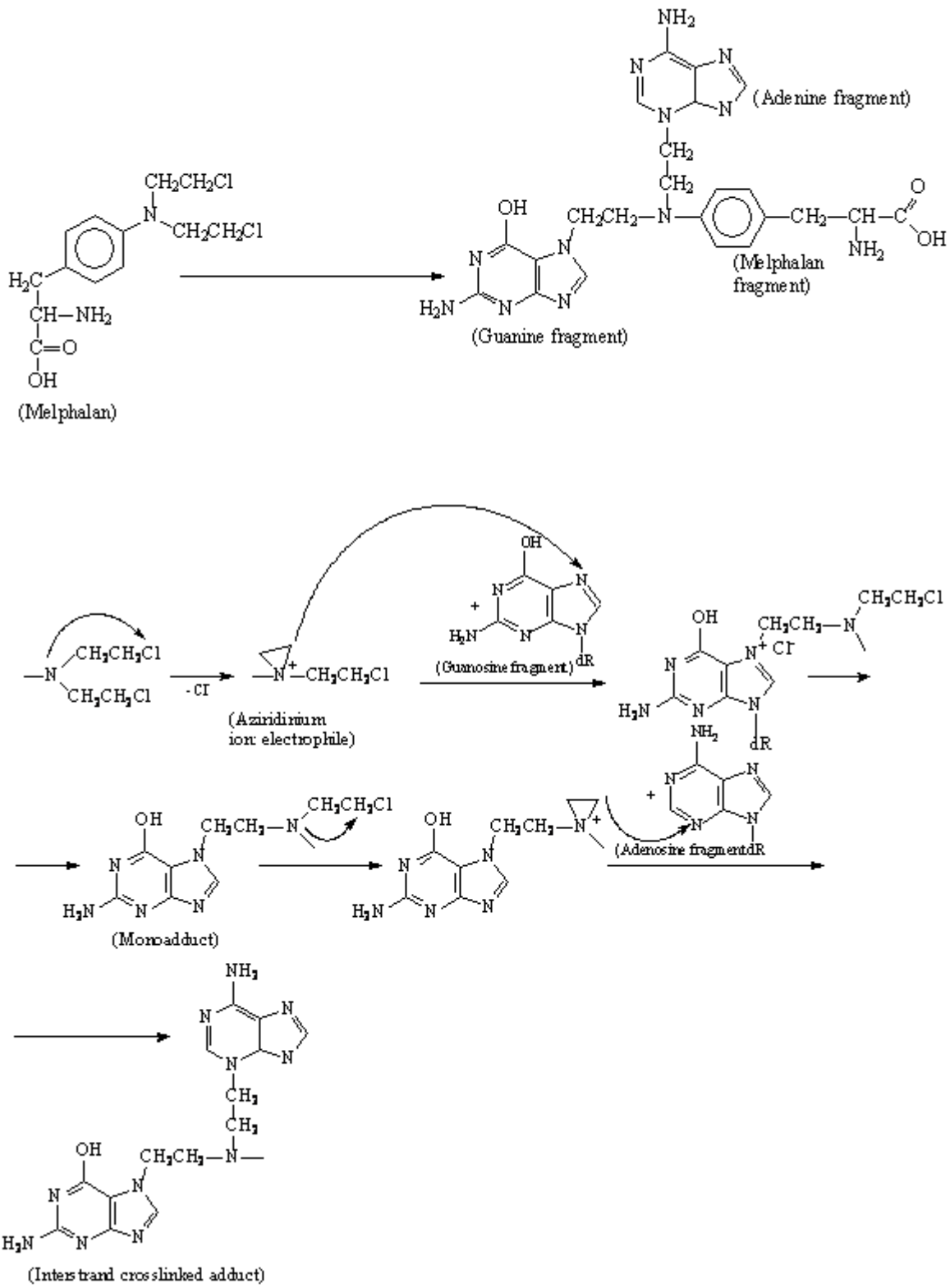
Description/applicability domain	
Mechanism	**S_N2 Alkylation, direct acting epoxides and related after cyclization**







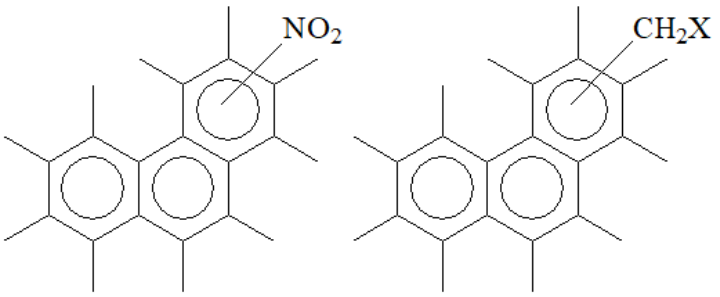
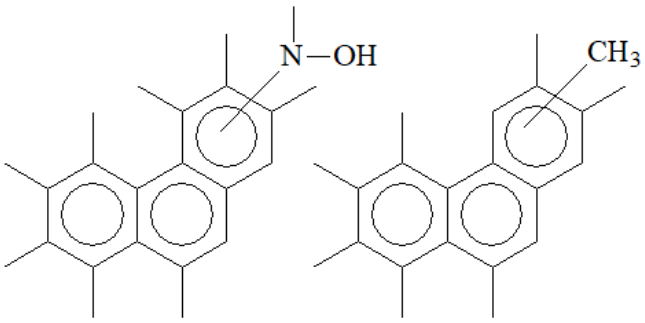
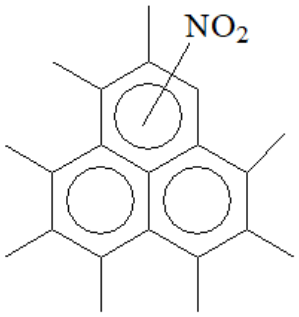
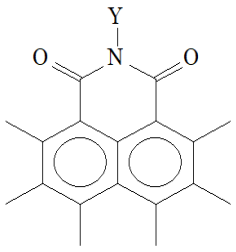
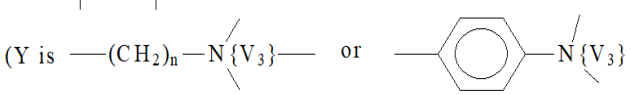
DNA adduct 2 (Phosphoester adduct)

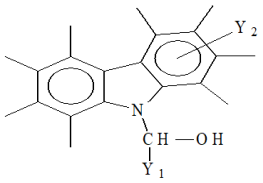
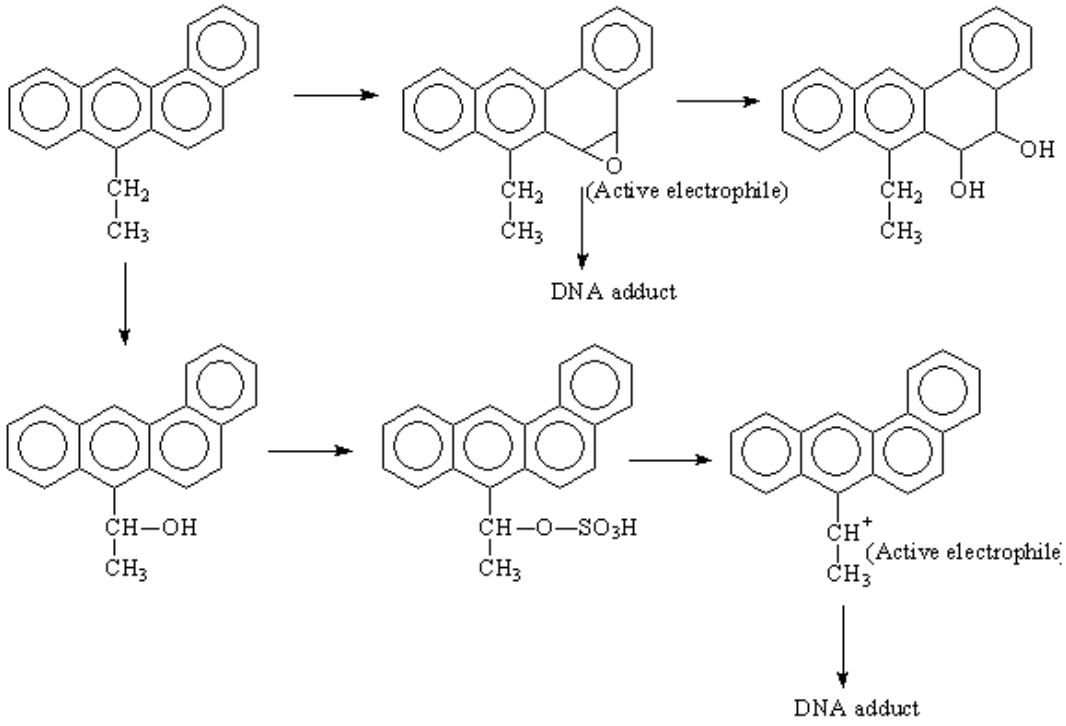


Set of chemicals used for profile development	Nitrogen and Sulfur Mustards
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Kovacic, P., J. D. Jacinto, *Mechanism of Carcinogenesis: Focus on Oxidative Stress and Electron Transfer*, Current Med. Chem. **8** (2001), 773

	– 796. 2. Hartley, J. A., J. P. Bingham, R. L. Souhami, DNA *Sequence Selectivity of Guanine-N7 Alkylation by Nitrogen Mustards is Preserved in Intact Cells*, Nucl. Acids Res. **20**(12), (1990), 3175 - 3178. 3. *Nitrogen Mustard*; http://en.wikipedia.org/wiki/Nitrogen_mustard. 4. Benedict, W. F., M. S. Baker, L. Haroun, *Mutagenicity of Cancer Chemotheraupetic Agents in the Salmonella/Microsome Test*, Canc. Res. **37** (1977), 2209 – 2213. 5. Alarcon, R. A., J. Meienhofer, E. Atherton, *Isophosphamide as a New Acrolein-Producing Antineoplastic Isomer of Cyclophosphamide*, Canc. Res. **32** (1972), 2519 – 2523. 6. DeMarini, D. M., H. N. Pham, A. J. Katz, H. E. Brockmann, *Relationship Between Structures and Mutagenic Potencies of 16 heterocyclic Nitrogen Mustards (ICR Compounds) in Salmonella typhimurium*, Mutat. Res. **136** (1984), 185 – 199. 7. Povirk, L. F., D. E. Shuker, DNA *Damage and Mutagenesis Induced by Nitrogen Mustards*, Mutat. Res. **318** (1994), 205 – 226. 8. Cahill, P. A., A. W. Knight, N. Billinton, M. G. Barker, L. Walsh, P. O. Keenan, C. V. Williams, D. J. Tweats, R. M. Walmsley, *The GreenScreen Genotoxicity Assay: A Screening Validation Programme*, Mutag. **19**(2) (2004), 105 – 119. 9. *Chemical Carcinogenesis Research Information System (CCRIS)*; http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?CCRIS. 10. Stewart, D., E. Sass, L. Fritz, L. Sasser, *Toxicology Studies on Lewisite and Sulfur Mustard Agents: Mutagenicity of Lewisite in the Salmonella Histidine Reversion Assay*, U.S. Army Medical Research and Development Command, Ntis AD-A213102, 1989; http://www.osti.gov/scitech/servlets/purl/1086509) 11. Ashby, J., H. Tinwell, R. D. Callander, N. Clare, *Genetic Activity of the Human Carcinogen Sulphur Mustard Towards Salmonella and the Mouse Bone Marrow*, Mutat. Res., **257**(3) (1991**),** 307 - 311. 12. CCRIS: Sulfur Mustard, Toxicology Data Network, U.S. National Library of Medicine; http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+ccris:@term+@rn+505-60-2 13. Wattana, M., T. Bey, *Mustard Gas or Sulfur Mustard: An Old Chemical Agent as a New Terrorist Threat*, Prehospital and Disaster Medicine **24**(1) (2009), 19 – 29.

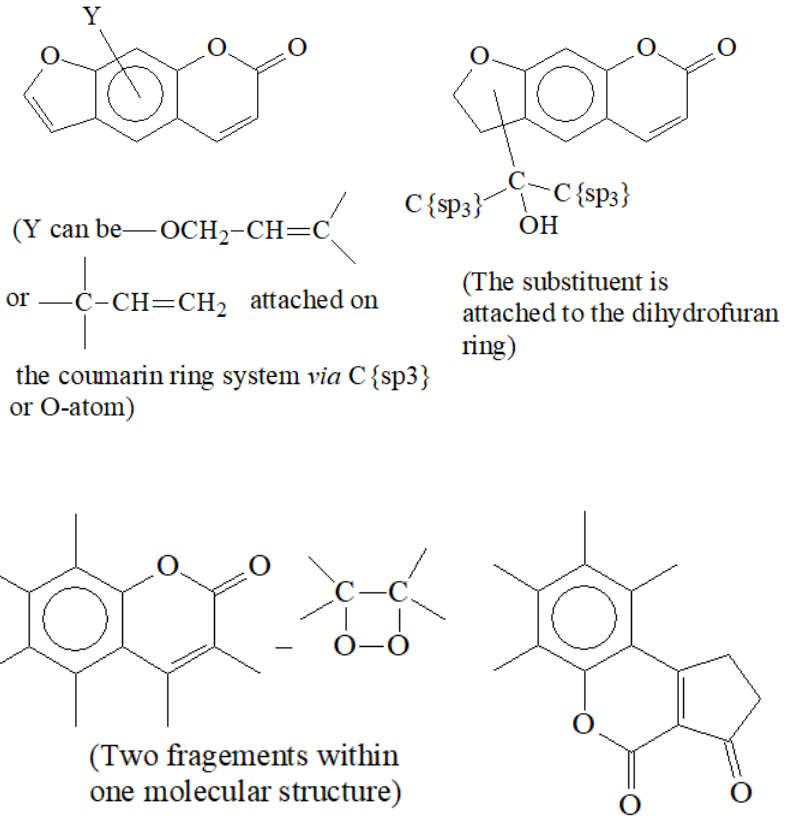
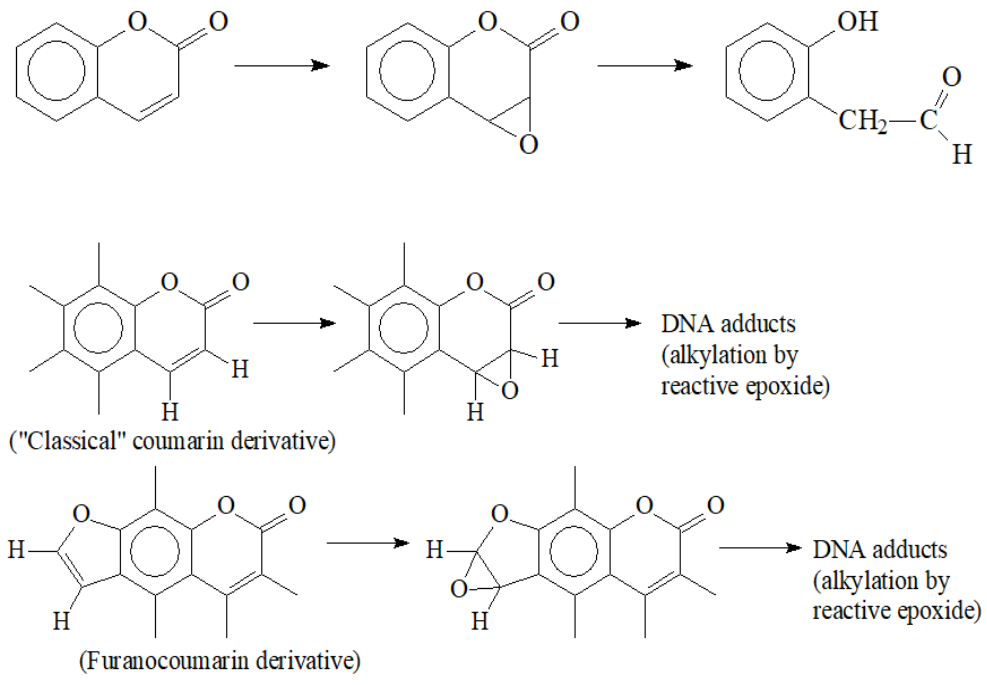
Individual profile/alert	
Name	Polycyclic Aromatic Hydrocarbon and Naphthalenediimide Derivatives
Type of profile	Structural alert

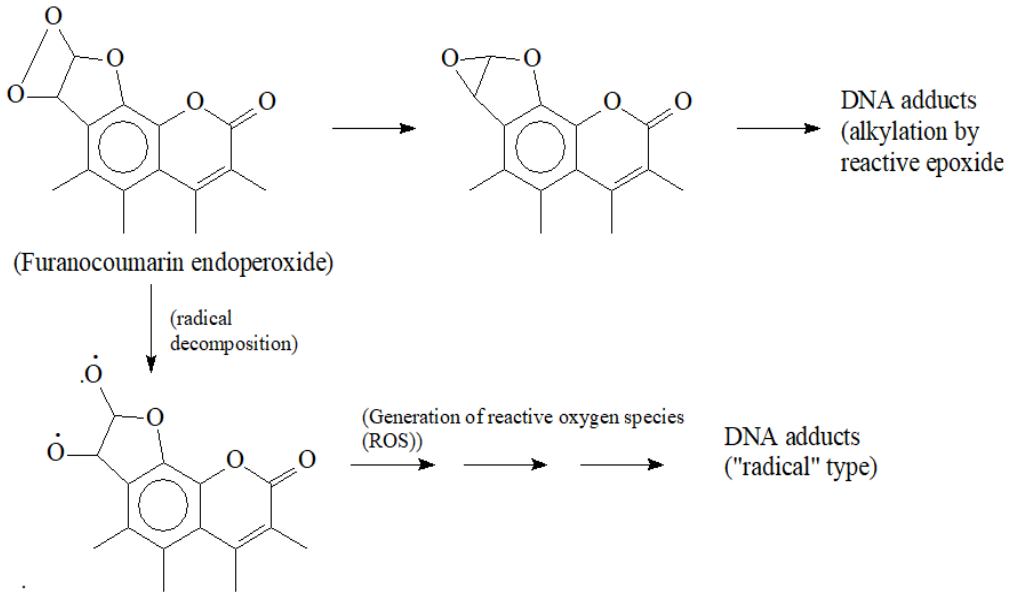
Description/applicability domain	 (X is Cl, Br)   (The substituents can be attached anywhere) **Typical PAH derivatives**   (n = 2 or 3) No more than two fused benzene rings; No -C(O)O-, -C(O)NH- or -SO_3H groups attached **Naphthaleneimide derivatives**

	 (Y_1 is –H or –CH_3; Y_2 is –H or –CH_3 (number of –CH_3 groups 1 or 2, can be attached anywhere); or –H (all); No other substituents) **Carbazole derivatives**
Mechanism	**S_N2 Alkylation, direct acting epoxides and related after P450-mediated metabolic activation, S_N1Alkylation after metabolically formed carbenium ion species and Non-covalent interactions DNA intercalation**
	
Set of chemicals used for profile development	Polycyclic Aromatic Hydrocarbon, Naphthaleneimide and Carbazole Derivatives
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Low, L. K., N. Castagnoli, Jr., *Drug Biotransformations* (In Burger's Medicinal Chemistry, 4th Ed., Part I (The Basis of Medicinal Chemistry, John Wiley&Sons, Inc. 1979), pp. 107 - 226. 2. Weston, A., C. C. Harris, *Chemical Carcinogenesis* (Ch. 12 from Cancer Medicine, 5th Edition, Ed. By R. C. Bast, D. W. Kufe, R. E. Pollock, R. R. Weichselbaum, J. F. Holland, E. Frei, 2000); http://www.ncbi.nlm.nih.gov/books/NBK20839/ 3. Boroski, G. L., *Theoretical Study Related to the Carcinogenic Activity of Polycyclic Aromatic Hydrocarbon Derivatives*, J. Org. Chem. **64** (1999), 7738 – 7744. 4. Nagao, M., T. Yahagi, Y. Seino, T. Sugimura, N. Ito, *Mutagenicity of*

	Quinoline and Its Derivatives, Mutat. Res. **42** (1977), 335 – 342. 5. McKay, S., P. B. Farmer, P. D. Cary, P. L. Grover, *The Metabolism of 7-Etylbenz[A]anthracene by Rat Liver Microsomal Preparations*, Drug Metabol. Dispos. **15** (1987), 682. 6. Rinderie, St. J., S. D. Black, P. K. Sharma, *Comparative Metabolism In Vitro of a Novel Carcinogenic Polycyclic Aromatic Hydrocarbon, 1,2,3,4-Tetrahydro-7,12-Dimethylbenz[a]anthracene, and Its Two Regioisomeric B-Ring Fluoro Analogues*, Canc. Res. **52** (1992), 3035 – 3042. 7. Guengerich, F. P., J. B. Wheeler, Y. J. Chun, D. Kim, T. Shimada, P. Aryal, Y. Oda, E. M. Gilliam, *Use of Heterologously-Expressed Cytochrome P450 and Glutathione Transferase Enxymes in Toxicity Assays*, Toxicology **181 – 182** (2002), 261 – 264. 8. McKnight, R. E., *Insights Into the Relative DNA Binding and Preferred Binding Mode of Homologous Compounds Using Isothermal Titration Calorimetry (ITC)* (Ch. 6 in *Applications of Calorimetry in a Wide Context – Differential Scanning Calorimetry, Isothermal Titration Calorimetry and Microcalorimetry*), January 23, 2013; http://www.intechopen.com/books/applications-of-calorimetry-in-a-wide-context-differential-scanning-calorimetry-isothermal-titration-calorimetry-and-microcalorimetry/insights-into-the-relative-dna-binding-affinity-and-preferred-binding-mode-of-homologous-compounds-u). 9. Czerwinska, I., Sh. Sato, B. Juskowiak, Sh. Takenaka, *Interactions of Cyclic and Non-Cyclic Naphthalene Diimide Derivatives with Different Nucleic Acids*, Bioorg. & Med. Chem. **22** (2014), 2593 – 2601. 10. Liu, Z. R., K. H. Hecker, R. L. Rill, *Selective DNA Binding of (N-Alkylamine)-Substituted Naphthalene Imides and Diimides to G+C-Rich DNA*, J. Biomolec. Struct. And Dynamics **14**(3) (1996), 331 – 339 (Abstract); http://www.ncbi.nlm.nih.gov/pubmed/9016410. 11. LaVoie, E. J., G. Briggs, V. Bedenko, D. Hoffmann, *Mutagenicity of Substituted Carbazoles in Salmonella typhimurium*, Mutat. Res. **101** (1982), 141 – 150.

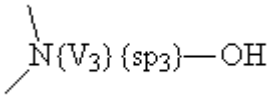
Individual profile/alert	
Name	Coumarins
Type of profile	Structural alert

Description/applicability domain	
Mechanism	**S_N2 Direct acting epoxides formed after metabolic activation, Radical ROS generation, Non-covalent interactions DNA intercalation & S_N1 DNA alkylation**
	

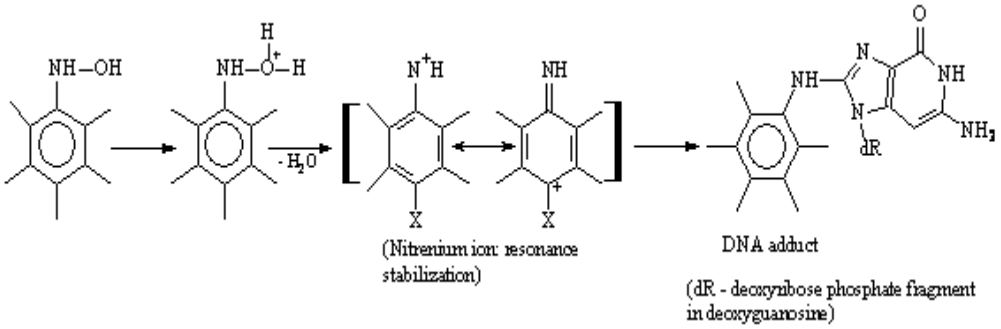


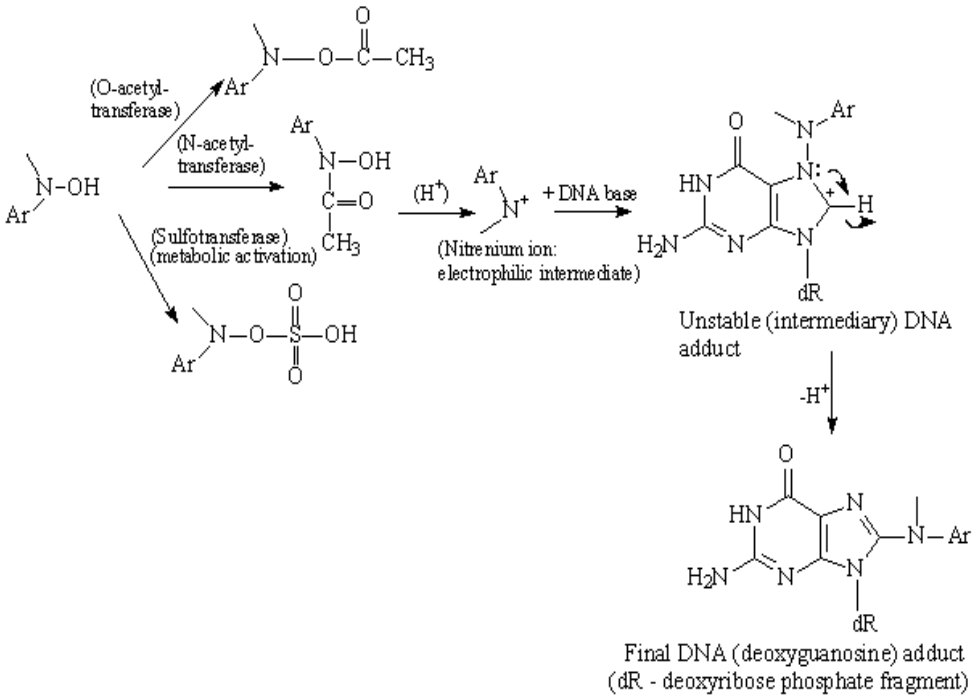
Set of chemicals used for profile development	Coumarins
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Kostova, I., Curr. Med. Chem. – Anti-Cancer Agents **5** (2005), 29 – 46. 2. *Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contacts with Food (AFC) on a Request from the Commission Related to Coumarin*, Question Number EFSA-Q-2003-118 (6 October 2004), The EFSA Journal **104** (2004), 1 – 36; https://www.efsa.europa.eu/en/efsajournal/pub/104, last visited 10.2019 . 3. Born, S. D., Drug Metab. Dispos. **30**(5) (2002), 483 – 487. 4. Lacy, A., Curr. Pharmac. Design **10** (2004), 3797 – 3811. 5. Zhou, S., Life Sci **74** (2004), 935 – 968. 6. *Function and Biotechnology of Plant Secondary Metabolites* (Ed. By M. Wink), Annual Plant Reviews, Vol 39, Willey-Blackwell 2010; https://onlinelibrary.wiley.com/doi/book/10.1002/9781444318876. Last visited 10.2019. 7. Quinto, I., Mutat. Res. **136** (1984), 49 – 54. 8. Uwalfo, A. O., J. Toxicol. Environ. Health: Current Issues **13**(4 – 6) (1984), 521 – 530. 9. Adam, W., Quimica Nova **16**(4) (1993), 316 – 320. 10. *Chemical Carcinogenesis Research Information System (CCRIS)*; http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?CCRIS. 11. Raney, V. M., Chem. Res. Toxicol. **6** (1993), 64 – 68. 12. Loarca-Pina, G., Mutat. Res./Fundam. Molec. Mechanisms of Mutagenesis, **398** (1 – 2) (1998), 183 – 187.

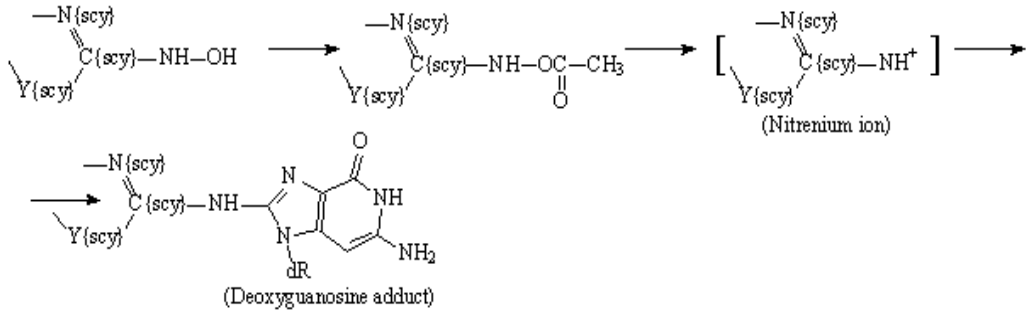
Individual profile/alert	
Name	N-Hydroxylamines

Type of profile	Structural alert
Description/applicability domain	
Mechanism	**S_N1 Nucleophilic attack after nitrenium ion formation, Radical ROS formation after GSH depletion (indirect), S_N2 Acylation & A_N2 Carbamoylation after isocyanate formation**

1. Aromatic and Heterocyclic N-Hydroxylamines

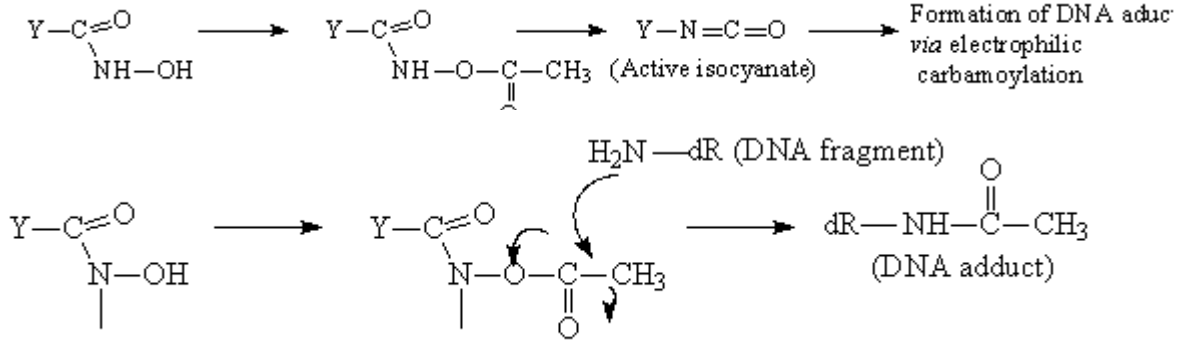




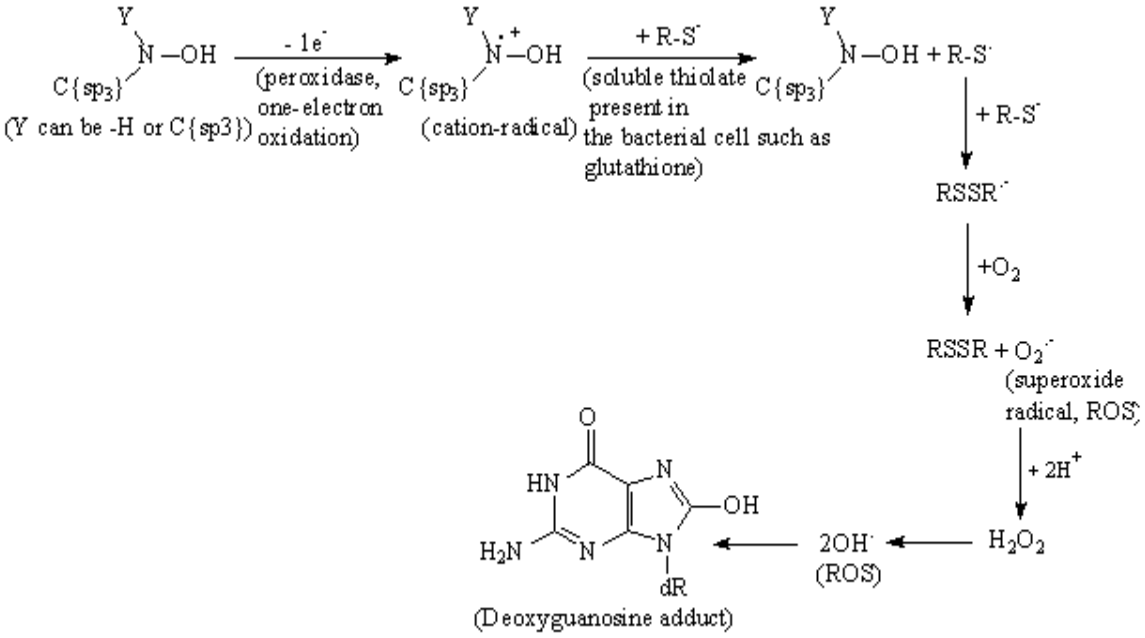


where Y{scy} can be heterocyclic N{V3} or S{V2}.

2 Hydroxamic Acids



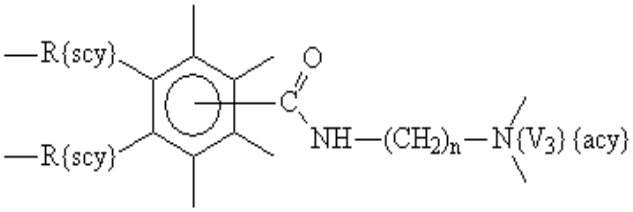
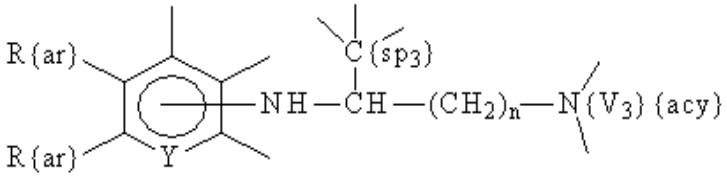
3. Other Non-Aromatic N-Hydroxylamines



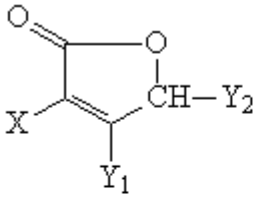
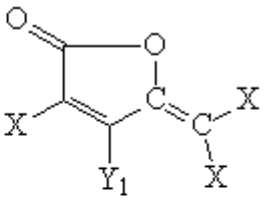
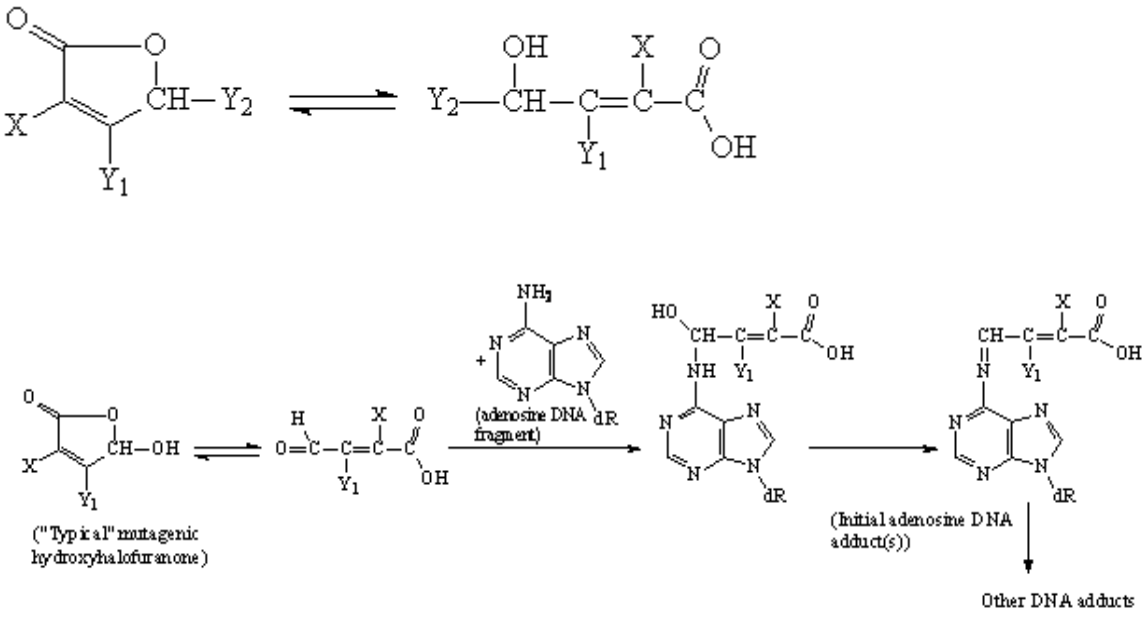
Set of chemicals used for profile development	N-Hydroxylamines
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Josephy P. D., M. Novak, *Reactive electrophilic metabolites of aromatic amine and amide carcinogens*, Front. Biosci.Scholar, S5(1) 2013, 341-359, DOI: 10.2741/S376. 2. Schut, H. A. J., Carcinog. 20, (3) (1999), 353 – 368. 3. Kalgutkar, A. S., Curr. Drug Metabol. **6**(3), 2005, 161 – 225). 4. Saito, K., Arch. Biochem. Biophys. **239**(1) (1985), 286 – 295. 5. Glatt, H., Carcinog. **25**(5) (2004), 779 – 786. 6. Mushtaq, A., J. Biol. Chem. **277**(14) (2002), 12175 – 12181. 7. Chung, K. T., Mutat. Res. **387** (1997), 1 – 16. 8. You, Z., Mutat. Res. **319** (1993), 19 – 30. 9. *Chemical Carcinogenesis Research Information System (CCRIS)*; http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?CCRIS. 10. Kato, R., Environ. Health Persp. **49** (1983), 21 – 25. 11. Barnes, W. S., Carcinog. **6**(3) (1985), 441 – 444.

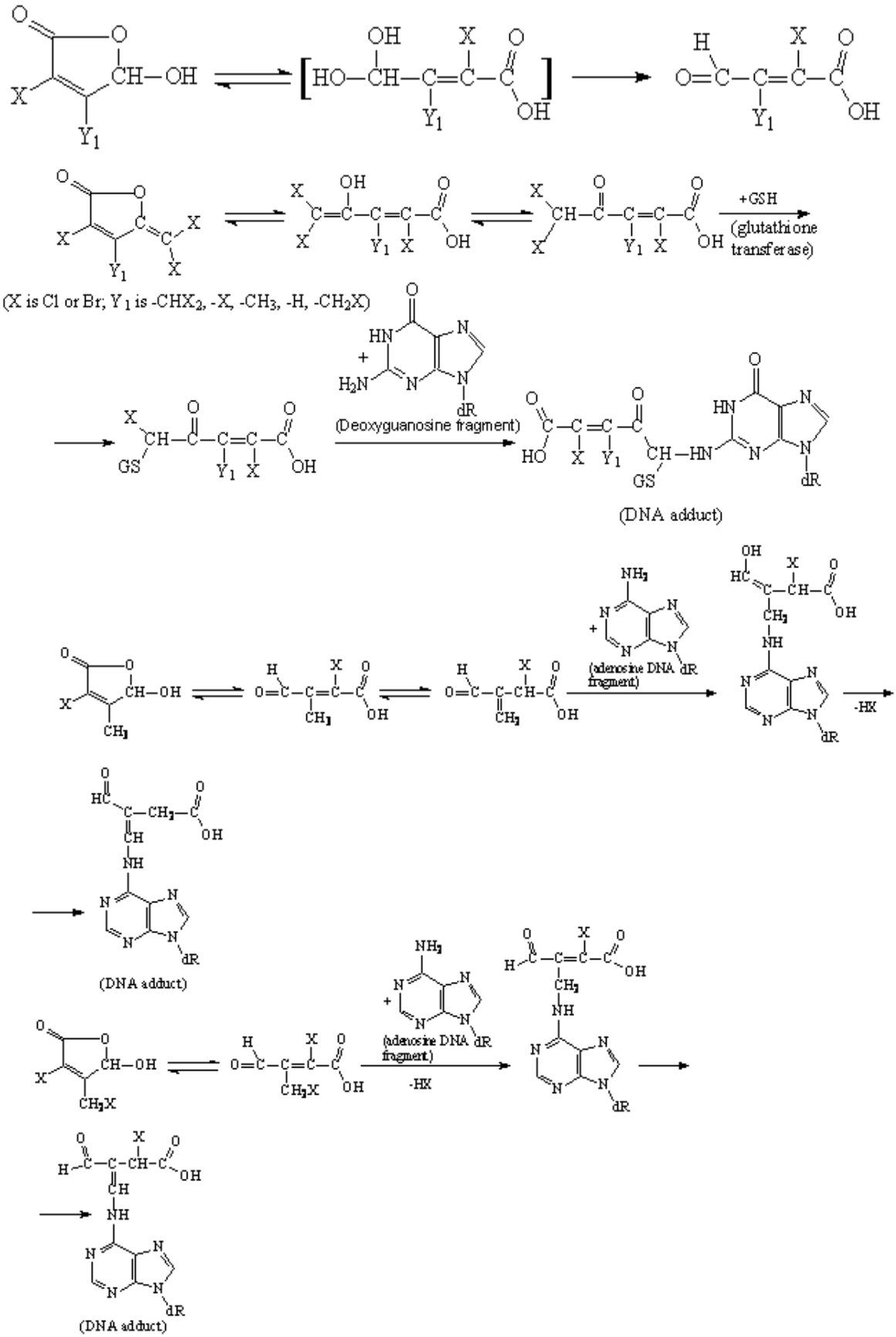
	12. Jaen, J. C., Eur. J. Med. Chem. **28** (1993), 547 – 553. 13. Herman, A., Carcinogenesis **20** (3) (1999), 353 – 368. 14. Shamovsky, I., JACS **133** (2011), 16168 – 16185. 15. Glatt, H., *Sulfation and Sulfotransferases 4: Bioactivation of Mutagens via Sulfation* FASEB J. **11**(5) (1997), 314 – 321. 16. Franke, R., Carcinogenesis **22**(9) (2001), 1561. 17. Beland, FR., Mutat. Res. **376** (1997) 13 – 19. 18. Wang, Ch. Y., Mutat. Res. **56** (1977) 7 – 12. 19. Wang, Ch. Y., Antimicrob. Agents Chemother. **11**(4) (1977), 753 – 755. 20. Skipper, P. L., Canc. Res. **40** (1980), 4704 – 4708. 21. Enoch, S. J., Mutat. Res. **743** (2012) 10 – 19. 22. Pai, V., Mutat. Res. **151** (1985), 201 – 207. 23. *General Discussion of Common Mechanisms for Aromatic Amines*, IARC Monographs, Vol. 99 (2010); ISBN-13 (PDF): 978-92-832-1599-8. 24. Spooren, A. M., Molecules and Diseases **26**(4) (2000), 373 – 386. 25. Kono, Y., Arch. Biochem. Biophys. **186**(1) (1978), 189 – 195. 26. Subrahmany, V. V., Chem.-Biol. Interactions **56** (1985), 185 – 199. 27. Makena, P. SEnviron. Molec. Mutagenesis **48** (2007), 404 – 413. 28. NTP Results Report: Results, Status and Publication Information of All NTP Chemicals Produced from Chemtrack System (08/10/00); https://echa.europa.eu/cs/registration-dossier/-/registered-dossier/16982/7/7/2, last visited 09.2019. 29. *3,4-Dichloroaniline*, The MAK Collection for Occupational Health and Safety, 19 June 2013; http://onlinelibrary.wiley.com/doi/10.1002/3527600418.mb9576e4013/pdf, last visited 09.2019.

Individual profile/alert	
Name	DNA Intercalators with Carboxamide and Aminoalkylamine Side Chain
Type of profile	Structural alert

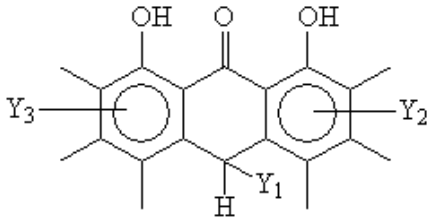
Description/applicability domain	 (n = 1 - 3; R{scy}: any atom in a cyclic (including aroma fragment condensed also with the aromatic ring)  (Y is N or C)
Mechanism	**Non-covalent interactions DNA intercalation**
Although most chemicals, capable of causing damaging genetic changes possess the ability to react chemically, more exactly, with formation of covalent bonds with DNA, acridines typically interact "physically", forming drug-DNA complexes by reversible binding. Thus the term "frameshift" or "acridine" mutagenesis can be restricted to genotoxic events that do not require covalent DNA binding. Linkage of an acridine chromophore to a basic side chain increases DNA binding affinity under physiological conditions. This is the case with the series of 9-aminoacridine carboxamide derivatives with a basic side chain, for which mutagenicity is strongly related to DNA intercalation of the acridine chromophore. The multi-cyclic planar structure and conjugation effects contribute to the positive mutagenicity effect [1, 5]. According to another publication, being less basic than aminoacridines, acridine carboxamides are weaker DNA binders [2]. The principal *in vitro* and *in vivo* metabolism of this class of chemicals is associated with the formation of acridones, and oxidative N-dealkylation and N-oxidation of the carboxamide side chain [3, 4]. This also contributes to the intercalating capability, genotoxic and carcinogenic properties of these chemicals [3, 4]. As far as some alkylaminoacridines are concerned, the results of the bacterial mutagenicity assays showed a very weak mutagenic effect of three drugs from this sub-category (chloroquine, primaquine and amodiaquine) in *Salmonella* strains TA97a and TA100, both with and without S9 mix [6]. Chloroquine is both the DNA intercalating agent and topoisomerase II inhibitor, which is positive in both the Ames and CA tests [7 - 10]. The size of the 8-aminoquinoline ring system suggests that, similarly to chloroquine, primaquine is able to intercalate into DNA and may act as a weak topoisomerase II inhibitor[11, 12].	
Set of chemicals used for profile development	DNA Intercalators with Carboxamide and Aminoalkylamine Side Chain
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Ferguson, L. R., Mutag. **5**(6) (1990), 529 – 540.

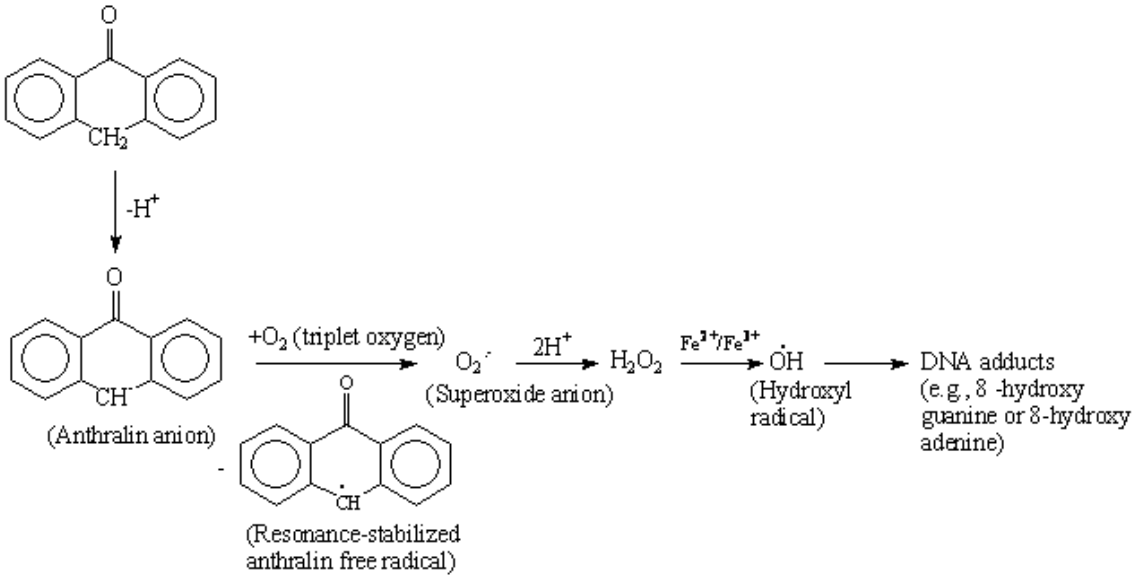
	2. Hicks, K. O., J. Phrarmacol. Exper. Ther. **297** (2001), 1088 – 1098. 3. Schlemper, B., Xenobiotica **23**(4) (1993), 361 – 371. 4. Schofield, Ph. C., Canc. Chemother. Pharmacol. **44** (1999), 51 – 58. 5. Ferguson, L. R., Eur. J. Canc. **26**(6) (1990), 700 – 714. 6. Chatterjee, T., *Mutagenesis*, **1998**, 13(6), 619 – 624. 7. Ferguson, L. R., Mutat. Res. **623** (2007), 14 – 23. 8. Snyder, R. D., Environ. Molec. Mutag. **51** (2010), 800 – 814. 9. Snyder, R. D., Mutat. Res. 609 (2006), 47 – 59. 10. Shubber, E. K., Cell Biol. Toxicol. **2**(3) (1986), 379 – 399. 11. Allison, R. G., Agents Chemother. **11**(12) (1977), 251 – 257. 12. Langer, S. W., Clin. Canc. Res. **5** (1999), 2899 – 2907.

Individual profile/alert	
Name	Halofuranones
Type of profile	Structural alert
Description/applicability domain	 **(I)**  **(II)** (X is Cl or Br; Y_1 is $-CHX_2$, -X, $-CH_3$, -H, $-CH_2X$; Y_2 is -H or -OH)
Mechanism	**S_N2 Nucleophilic substitution at sp3 carbon atom & A_N2 Shiff base formation**
 ("Typical" mutagenic hydroxyhalofuranone) (adenosine DNA fragment) (Initial adenosine DNA adduct(s)) Other DNA adducts	

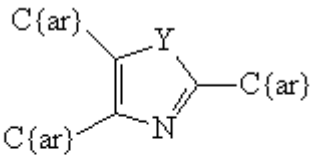

+GSH
(glutathione transferase)
(X is Cl or Br; Y1 is -CHX2, -X, -CH3, -H, -CH2X)
(Deoxyguanosine fragment)
(DNA adduct)
(adenosine DNA fragment)
-HX
(DNA adduct)
(adenosine DNA fragment)
-HX
(DNA adduct)

Set of chemicals used for profile development	Halofuranones
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Woo, Y. T., Environ. Health Persp. **110** (Suppl. 1) (2002), 75-87. 2. Tuppurainen, K. *A Plausible Mechanism for the Mutagenic Activity (Salmonella typhimurium TA100) of MX Compounds: A Formation of CG-CG^{+}-CG Radical Cation by One-Electron Reduction*, SAR and QSAR in Environ. Res. **7**(1-4) (1997), 281 – 286. 3. Bombarelli, R. G., Env. Sci. Technol. **45** (2011), 9009 – 9016. 4. Bombarelli, R. G., Environ. Sci Technol. **46** (2012), 13463 – 13470. 5. Anders, M. W., Drug Metabol. Rev. **36** (3 – 4) (2004), 583 – 594. 6. Bombarelli, R. G., *Chemical Processes That Can Damage Cellular DNA: Reactivity and Alkylating Potential of Some O-Heterocycles*, PhD Thesis, Departamento de Quimica Fisica Facultad de Ciencias Quimicas, Salamanca, December 2011; http://web.usal.es/~jucali/papers/PHD20111.pdf. Last visited 10.2019

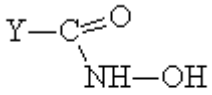
Individual profile/alert	
Name	Anthrones
Type of profile	Structural alert
Description/applicability domain	 (Y_1 can be —H or —C(=O)—$(CH_2)_nH$ (n = 1 - 3) Y_2, Y_3 can be -H or $-CH_3$ or $-OCH_3$ or their combinations)
Mechanism	**Radical mechanism by ROS formation (indirect)**



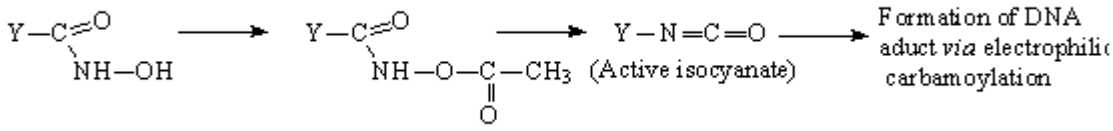
Set of chemicals used for profile development	Anthrones
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Muller, Gen. Pharmac. **27**(8) (1996), 1325 – 1335. 2. Mannisto, Arch. Toxicol. **59** (1986), 180 – 185).

Individual profile/alert	
Name	Triarylimidazole and Structurally Related DNA Intercalators
Type of profile	Structural alert
Description/applicability domain	 (Y can be N{V3}{sp3}, -S-{V2}, -O-) (C{ar}: carbon atom as part of arene ring)
Mechanism	**Non-covalent interactions DNA intercalation**
The chemical mechanisms accompanied by the formation of a covalent adducts are expected to be characteristic for *Salmonella typhimurium* strains, related to base pair substitutions (strains TA100, TA102 and TA1535). However, DNA intercalations operate with the strains associated with induction of frameshift mutations (TA97, TA98, TA1537 and TA1538). Substituted triphenylimidazoles were suggested to belong to the class of DNA intercalating agents [1], probably due to the multi-cyclic planar molecular system and conjugation effects.	
Set of chemicals used for	Triarylimidazole and Structurally Related DNA Intercalators

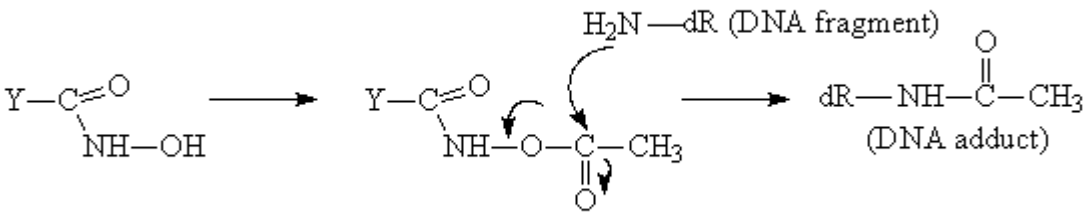
profile development	
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Enoch, Mutat. Res. **743** (2012), 10 – 19. 2. Mercangoz, A., B. A. Tuylu, *Detection of Mutagenic Effects of 2*,4,5-Trisubstituted *Phenyl Imidazole and Its Derivatives in Ames/Salmonella/Test System*, Turk. J. Biol. **24** (2000), 57 – 64 (Abstract); http://journals.tubitak.gov.tr/biology/issues/biy-00-24-1/biy-24-1-5-96048.pdf.

Individual profile/alert	
Name	Hydroxamic Acids
Type of profile	Structural alert
Description/applicability domain	 (Y can be C, N or C-O-)
Mechanism	**A_N2 Carbamoylation after isocyanate formation and S_N2 Acylation**

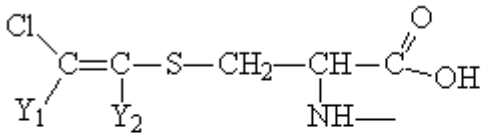
A number of pyridine and quinoline carbohydroxamic acids have been tested for mutagenicity on *Salmonella typhimurium* strains TA100 and TA98. According to the authors, the mechanism for the mutagenicity of hydroxamic acids is associated with the so-called *Lossen rearrangement* of the acid conjugates produced by enzymatic acylation of the hydroxamic acids, followed by carbamoylation of the target (DNA) molecule by the resulting isocyanate [4].

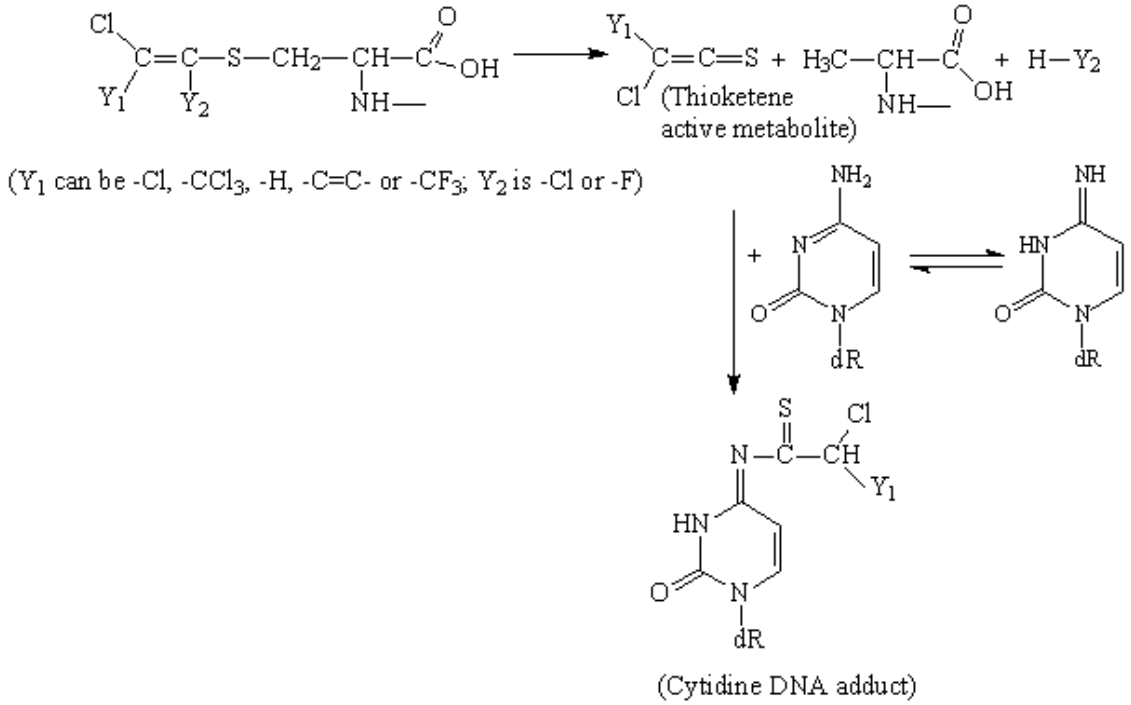


Another possible mechanism may involve enzymatic activation (O-acylation) and subsequent acylation reaction with DNA for acetohydroxamic acid derivatives (Y is alkyl, O-alkyl or N-alkyl) [5]:



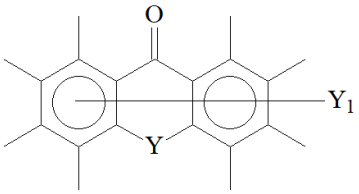
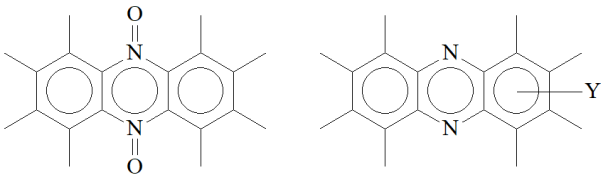
Set of chemicals used for profile development	Hydroxamic Acids
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Wang, Mutat. Res. **56** (1977) 7 – 12. 2. Wang, Antimicr. Agents Chemother. **11**(4) (1977), 753 – 755. 3. Skipper, Canc. Res. **40** (1980), 4704 – 4708. 4. Kochany, Mutat. Res. **135** (1984), 139 – 148. 5. Enoch, Mutat. Res. **743** (2012) 10 – 19.

Individual profile/alert	
Name	Haloalkene Cysteine S-Conjugates
Type of profile	Structural alert
Description/applicability domain	 (Y_1 can be -Cl, $-CCl_3$, -H, -C≡C- or $-CF_3$; Y_2 is -Cl or -F)
Mechanism	**A_N2 Nucleophilic addition to metabolically formed thioketenes**

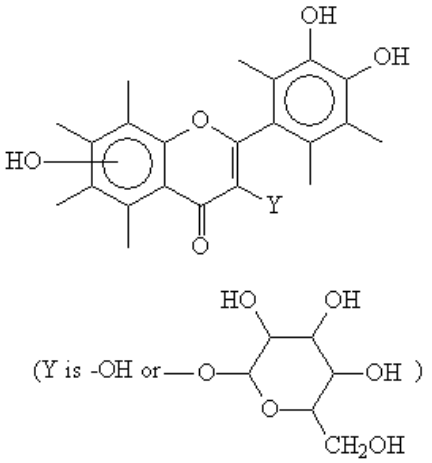


Set of chemicals used for profile development	Haloalkene Cysteine S-Conjugates
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. *Evidence on the Carcinogenicity of 1,3-Hexachlorobutadiene* (Final), December 2000, Reproductive and Cancer Hazard Assessment Section Office of Environmental Health Hazard Assessment California Environmental Protection Agency; https://oehha.ca.gov/media/downloads/proposition-65/chemicals/hcbd-final.pdf, last visited 09.2019 2. Dreessen, Mutat. Res. **539** (2003), 157 – 166. 3. Vamvakas, Chem.-Biol. Interact. **65** (1988), 59 – 71. 4. Muller, Chem. Res. Toxicol. **11** (1998), 464 – 470.

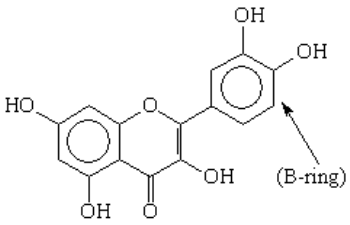
Individual profile/alert	
Name	Acridone, Thioxanthone, Xanthone and Phenazine Derivatives
Type of profile	Structural alert

Description/applicability domain	 (Y is O, S{V_2}, N{V_3}) (Y_1 can be -OH, -O-CH_3, -NH{{sp3}{V3}, -CH_3, -CH_2OH,  No other substituents allowed, except for -H total number of substituents in both benzene rings: 2 - 5) (Note: Such substituents are believed to promote intercalation effects, due to electron-donating capability and/or enhanced conjugations)  (Y can be combinations between -H and -NH_2 or -H, NH_2 and -OH or OCH_3)
Mechanism	**Non-covalent interactions DNA intercalation and Radical ROS generation (indirect)**
A number of tricyclic acridone, thioacridone and thioxanthene derivatives are known to act as DNA intercalating agents and possess *in vitro* bacterial mutagenicity in a broad range of intensity. Generally, acridones showed the highest bacterial mutagenicity [1]. All intercalating agents contain, as an important requirement, a planar electron-rich structural fragment. In such a case, binding to DNA is enhanced when there is substituent bearing, for example, an amino group, which can bind electrostatically to the phosphate groups of DNA. Thus planar tricyclic and tetracyclic ring systems can be accommodated between the successive base pairs of DNA [5]. With the frameshift mutations, base pairs relative to the original sequence are gained or lost, and the reading frame of genetic code is altered. Frameshift mutagens may stimulate the induction of mutations by covalent or non-covalent interactions. For example, acridine compounds are the most familiar frameshift mutagens, that intercalate between DNA base pairs. Intercalation is sufficient for mutagenesis, since, for example, chemicals such as 9-aminoacridine: The phenazine di-N-oxide derivative myxin was found to cause DNA strand cleavage under aerobic conditions which could result either from deoxygenative metabolism or from redox cycling. Redox cycling has the potential to generate reactive oxygen species (ROS), including the DNA-cleaving hydroxyl radical. Thus one-electron bioreductive activation of aromatic N-oxides can be assumed, which might cause genotoxic effects [9].	
Set of chemicals used for profile development	Acridone, Thioxanthone, Xanthone and Phenazine Derivatives
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Denny, Mutat. Res. **232** (1990), 233 – 241. 2. Matsushima, Mutat. Res. **150** (1985), 141 – 146.

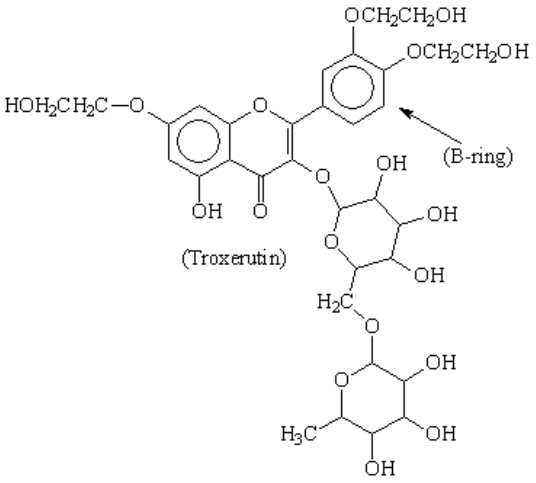
	3. Harman, Mutat. Res./Environ. Mutag. Rel. Subjects **31**(2) (1975), 87 – 95. 4. Feng, J. Pharm. Biomed. Anal. **62** (2012), 228 – 234. 5. Double, J. Pharm. Pharmac. **28** (1976), 166 – 169. 6. Hoffman, Res. Toxicol. **10**(4) (1997), 347 – 359. 7. Sarrif, Mutat. Res. **321** (1994), 43 – 56. 8. Watanabe, Mutat. Res. **227** (1989), 135 – 145. 9. Chowdhury, Chem. Res. Toxicol. **25** (2012), 197 – 206.

Individual profile/alert	
Name	Flavonoids
Type of profile	Structural alert
Description/applicability domain	
Mechanism	**A_N2 Michael-type addition, quinoid structures and Radical ROS generation (indirect)**

Certain structural requirements should be fulfilled for direct bacterial mutagenicity. For example, the flavonoid derivative, troxerutin, was not mutagenic, since the substitution of the two catechol hydroxyl group in quercetin with hydroxyethyl groups abolished mutagenicity [3]. According to another study, only those flavonols either lacking or possessing one B-ring hydroxyl group have an absolute requirement for microsomal (S9) activation. This requirement can be illustrated by the two flavonoids, quercetin (strong mutagen as parent chemical and, even more, mutagenic after metabolic activation), and troxerutin (non-mutagenic) [4]:

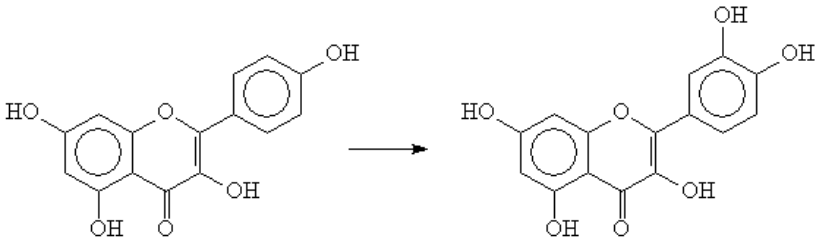


(Quercetin)



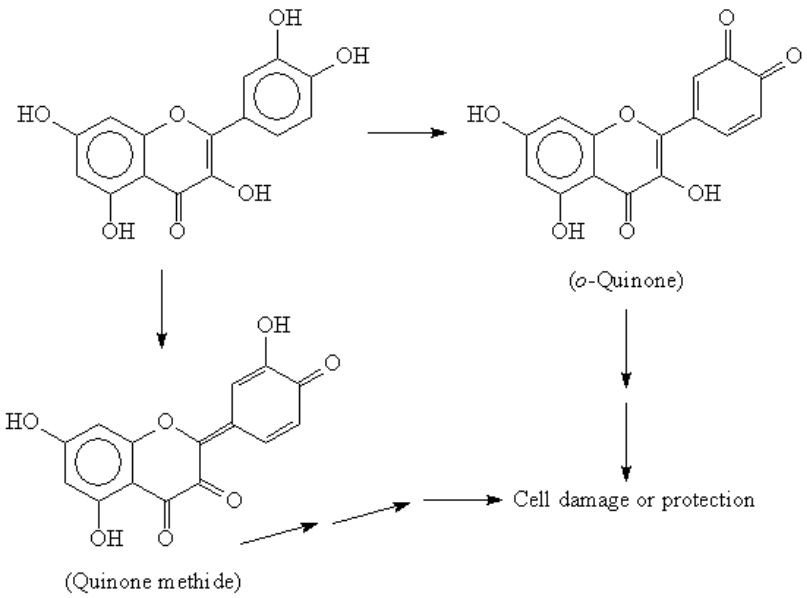
(Troxerutin)

Thus the two most mutagenic chemicals from this class were quercetin (see above, mutagenic as parent chemical) and kaemferol [4]. These compounds are also the most commonly occurring flavonoids in plants. Kaempferol, however, requires metabolic activation in order to form the active catechol-type metabolite which may, consequently, generate genotoxic *o*-quinone intermediate:



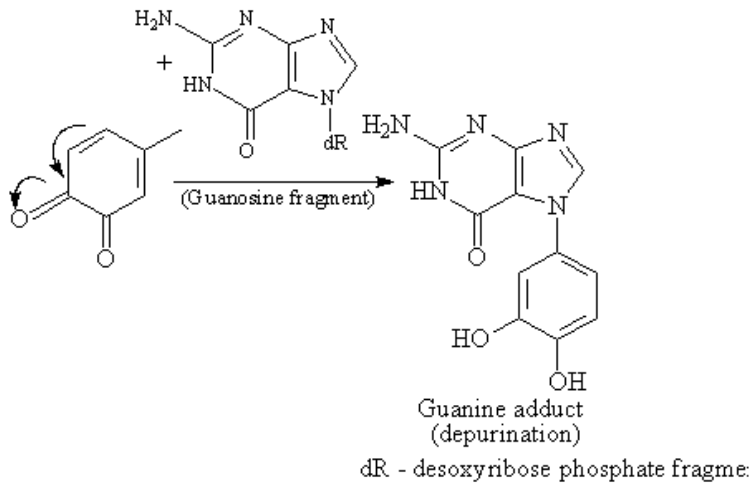
(Kaempferol)

For example, quercetin can generate active *o*-quinone/quinone methide metabolites by the following pathways [7]:

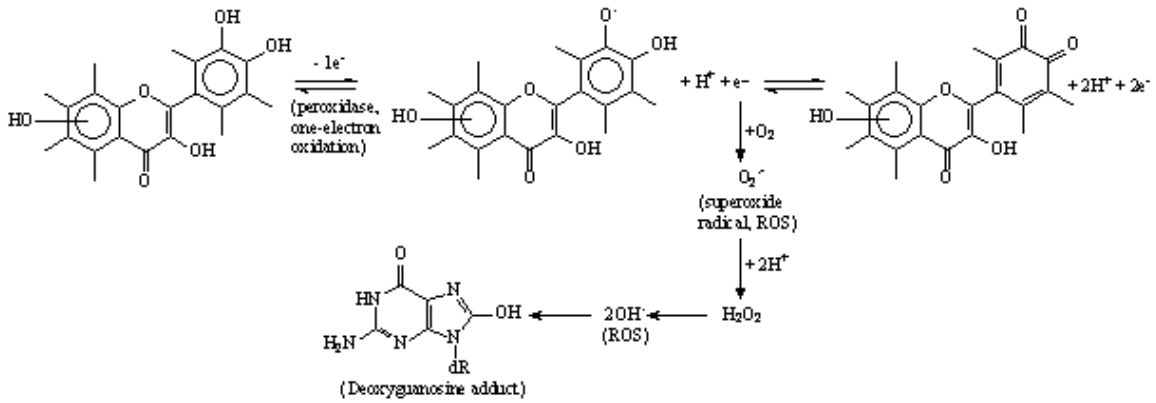


(Quinone methide)

The mutagenicity of quercetin is assumed to be partly due to the generation of such active metabolites. One possible mechanism for the formation of DNA adducts from *o*-quinones could involve depurination, due to Michael addition, according to the following scheme [8]:

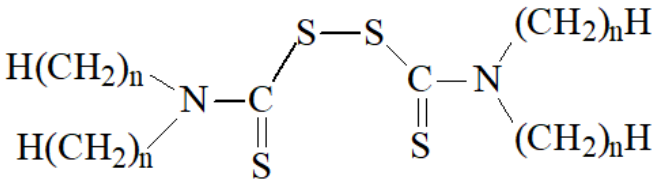
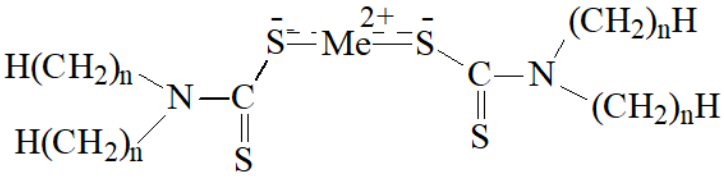
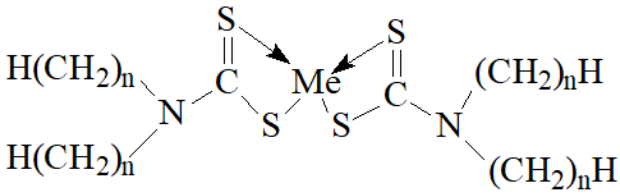
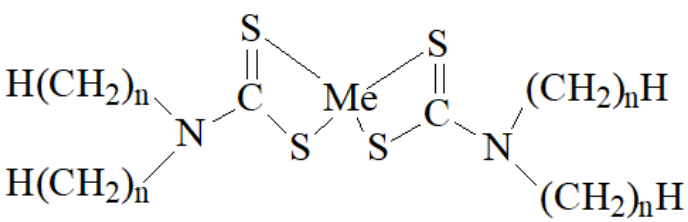


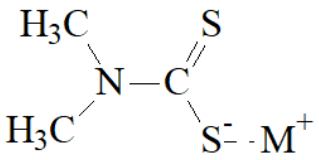
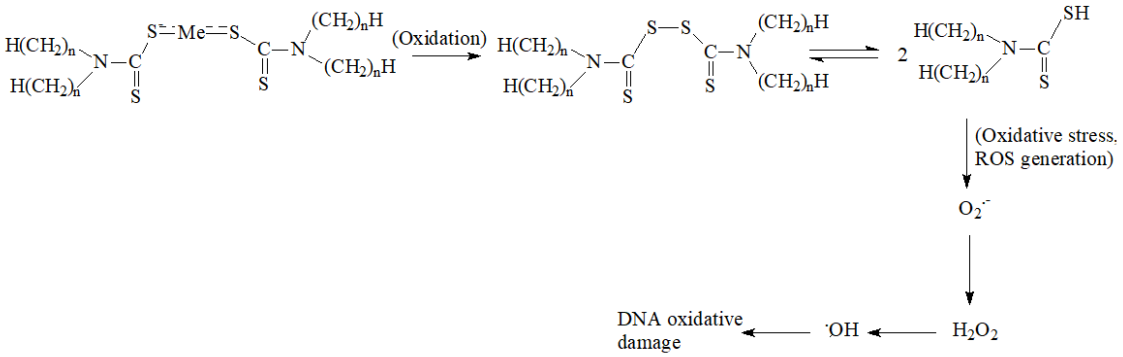
If the presence of endogenous peroxidase enzymes in the "classical" *Salmonella typhimurium* strains is assumed, the following mechanistic scheme involving the formation of ROS could explain the observed positive *in vitro* bacterial mutagenicity results for a few flavonoids such as quercetine as parent chemicals:

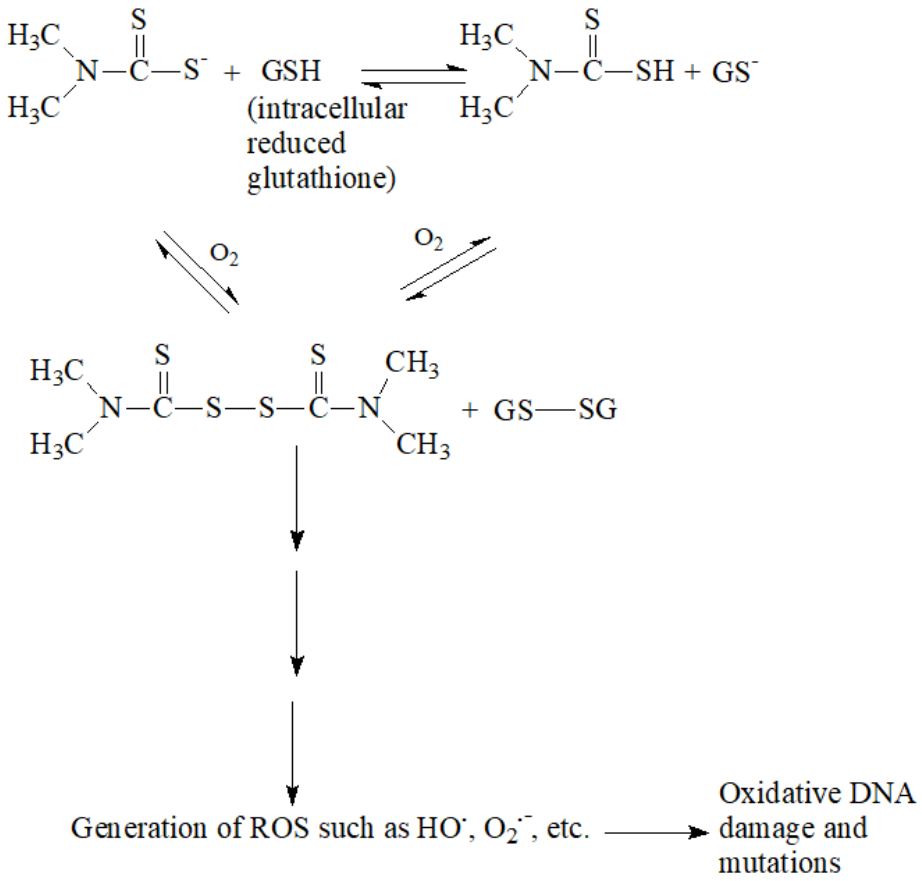


Set of chemicals used for profile development	Flavonoids
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Resende, Molecules **17** (2012), 5255 – 5268. 2. Yamashita, Mutat. Res. **425** (1999), 107 – 115. 3. Marzin, Toxicol. Lett. **35** (1987), 297 – 305. 4. Brown, Mutat. Res. **66** (1979), 223 – 240. 5. Appleton, Natural Medicine J. **2**(1) (2010), 1 – 6. 6. *Chemical Carcinogenesis Research Information System*

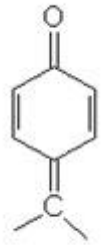
	(CCRIS); http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?CCRIS. 7. Spencer, J. P. E., G. G. C. Kunhle, R. J. Williams, C. R. Evans, *Intracellular Metabolism and Bioactivity of Quercetin and Its In Vivo Metabolites*, Biochem. J. **372** (2003), 173 – 181. 8. Li, Carcinogeneis **25**(2) (2004), 289 – 297. 9. Schweigert, Environ. Microbiol. **3**(2) (2001), 81 – 91. 10. Lang, Mutat. Res. **191** (1987), 139 – 143. 11. Subrahmany, Chem.-Biol. Interactions **56** (1985), 185 – 199.

Individual profile/alert	
Name	N,N-Dialkyldithiocarbamate Derivatives
Type of profile	Structural alert
Description/applicability domain	  or  or 

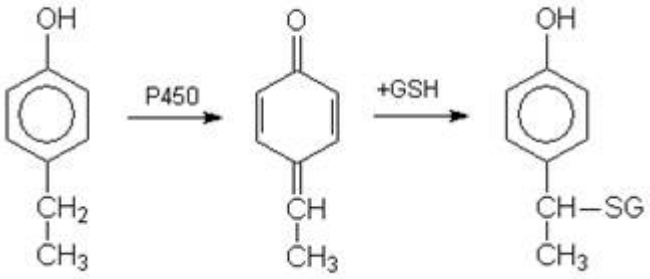
	(n = 1, 2; Me^{2+} can be Zn^{2+}, Cd^{2+}, Cu^{2+} or Pb^{2+} or Me can be Zn, Cd(II), Cu(II) or Pb(II) (depending on the structural representation of metal complexes))  (M^{+} can be Na^{+}, K^{+}, Li^{+})
Mechanism	**Radical ROS generation**
 Mutagenicity of tetramethylthiuram disulfide (thiram), which can be obtained by mild oxidation of dimethyldithiocarbamate has been experimentally proved for both frameshift and base-substitution sensitive strains of Salmonella typhimurium. The following reversible equilibrium and redox cycling effects seem to be established for the interaction of sodium dimethyldithiocarbamate with endogenous (intracellular) thiols such as glutathione under biological conditions:	



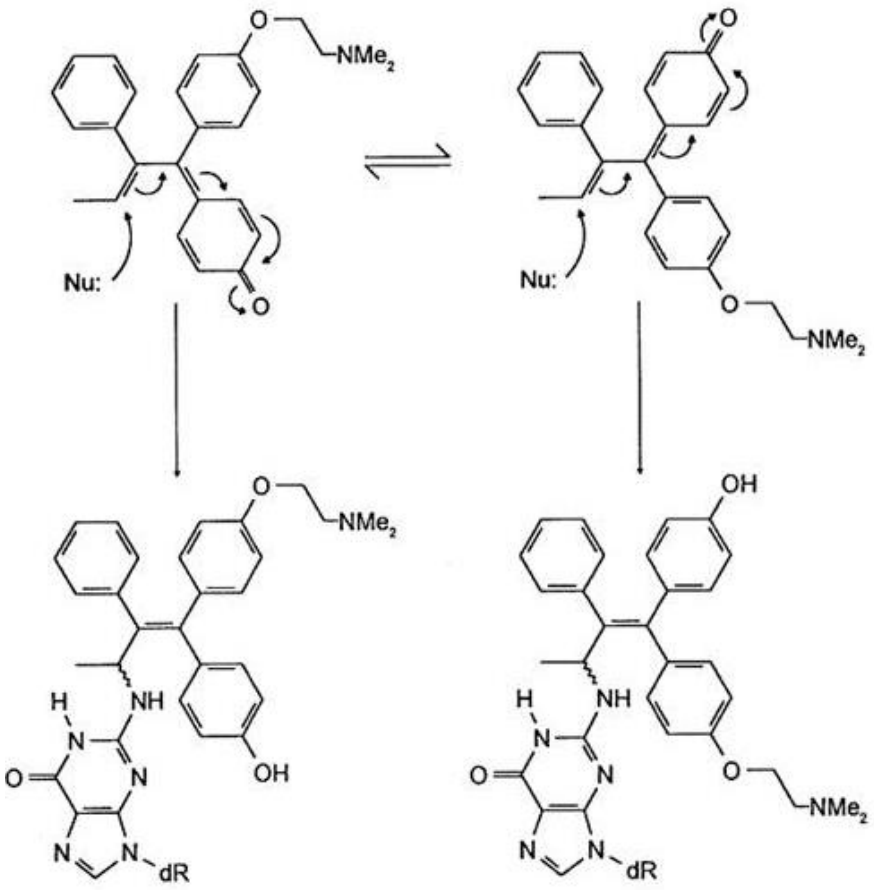
Set of chemicals used for profile development	N,N-Dialkyldithiocarbamate Derivatives
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Rannug, Chem. Biol. Interact. **49**(3), (1984), 329 - 340. 2. Franekic, Mutat. Res. **325**(2 - 3), (1994), 65 - 74. 3. Hedenstedt, Mutat. Res. **68**(4), (1979), 313 - 325. 4. Wild, Biochem. J. **338** (1999), 659 - 665. 5. Johnson, Toxicol. Sci **76**, (2003), 65 - 74. 6. Grebelli, Mutag. **12** (1992), 97 – 112. 7. Moriya, Mutat. Res./Environmental Mutagenesis and Related Subjects **54**(2) (1978), 221. 8. Staron, Arch. Toxicol. **86** (2112), 1841 – 1850. 9. CCRIS: *Sodium Dimethyldithiocarbamate RN 128-04-1*, Toxicology Data Network, U.S. National Library of Medicine**;** https://toxnet.nlm.nih.gov/cgi-bin/sis/search2, last visited 10.2019 10. *Test Plan Sodium Dimethyldithiocarbamate CAS Registry Number 128-04-1* Rubber and Plastic Additives Panel American Chemistry Council December 2003;

Individual profile/alert	
Name	Quinone methides
Type of profile	Structural alert
Description/applicability domain	
Mechanism	**Radical ROS formation after GSH depletion & Michael addition Quinone type compounds**

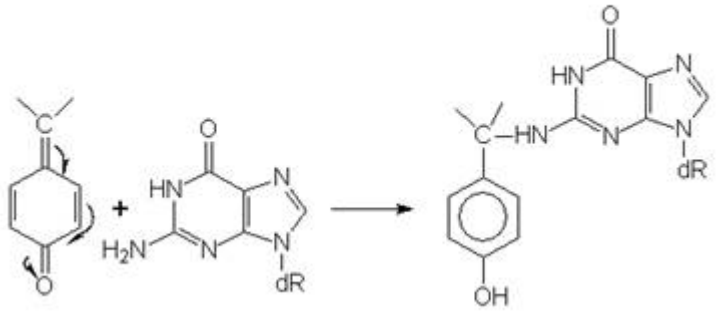
Results have demonstrated that a series of simple, sterically-unhindered alkylphenols are metabolized to reactive quinone methide intermediates by mammalian liver enzymes. This oxidation mechanism is regarded as common for an increasing number of *p*-alkylphenols and appears to play a significant role in their reported cytotoxic effects, mostly, by glutathione depletion. The following scheme of the formation of glutathione conjugates from 4-ethylphenol *via* quinone methide intermediate was suggested by these authors [3]:



Tamoxifen is a liver carcinogen in rats and has been shown to increase the risk of specific cancer in women. One of the proposed pathways for the metabolic activation of tamoxifen involves oxidation to 4-hydroxytamoxifen, which may be further oxidized to an electrophilic quinone methide intermediate. It was shown, that the quinone methide intermediate derived from 4-hydroxytamoxifen reacted with DNA to form covalent adducts. The major products, which resulted from 1,8-addition of the exocyclic nitrogen of deoxyguanosine in DNA to the conjugated system of the 4-hydroxytamoxifen quinone methide, were characterized as (*E*)- and (*Z*)-a-(deoxyguanosin-*N*2-yl)-4-hydroxytamoxifen, according to the following general scheme [4]:



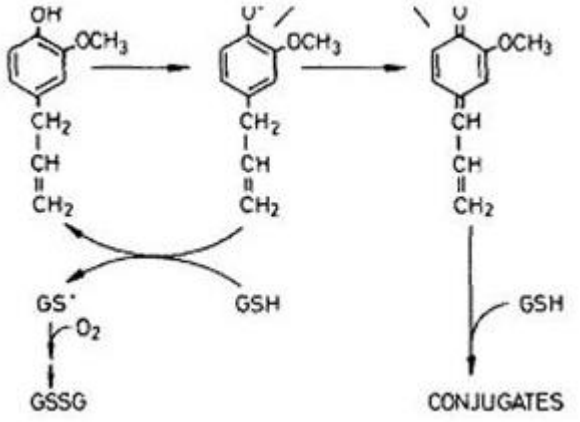
Therefore, based on the above data, the following general scheme of DNA reactivity, and the resulting mutagenicity effects of quinone methide structural fragments can be assumed:



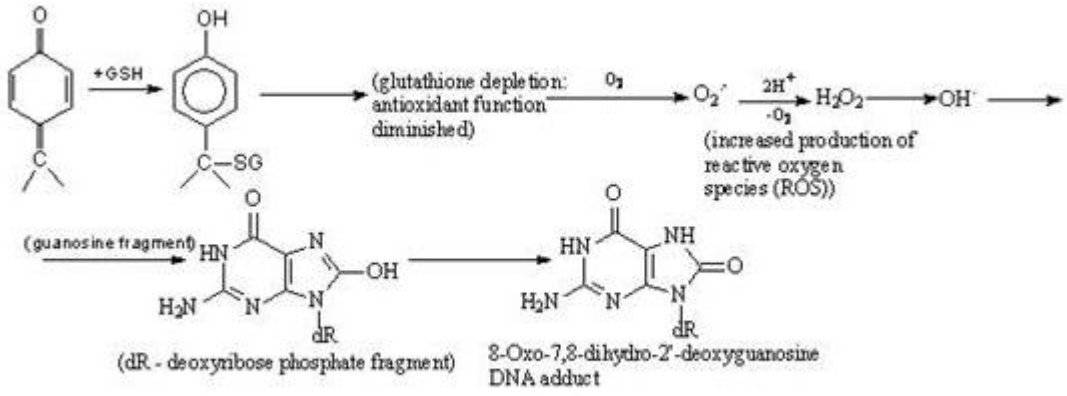
where dR represents desoxyribose fragment.

On the other hand, the compound eugenol (1-allyl-3-methoxy-4-hydroxybenzene) extracted from glove oil and marjoram, is widely used as a food flavouring substance and is present in spices such as basil, cinnamon and nutmeg. The genotoxicity of eugenol in V79 cells was evaluated with respect to chromosomal aberration effects. Eugenol was found to induce chromosomal aberration to a significant degree, and S9 liver fraction increased this effect in a dose-dependent manner. The results demonstrated that, the genotoxicity of eugenol was also associated with its topoisomerase II inhibiting activity [5]. Eugenol is known to form the intermediary quinone methide metabolite *by* the following

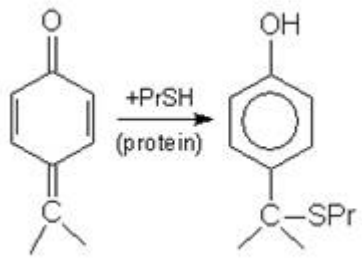
scheme [6]:



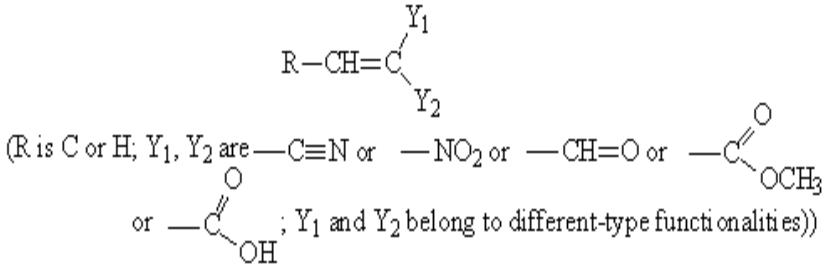
Quinone methide is highly-reactive, rapidly forming DNA adducts, and was indicated to also contribute to the induction of chromosome aberrations in V79 cells. Since V79 cells are devoid of CYP- 450 activity, the genotoxicity results could be due to the formation of reactive oxygen species (RSO), resulting from glutathione depletion. This was confirmed by the fact, that 8-hydroxy-20-deoxyguanosine DNA adduct can be produced by eugenol [5]. Therefore, another mechanism of DNA attack may be involved in the overall genotoxicity of quinone methide fragments as follows:



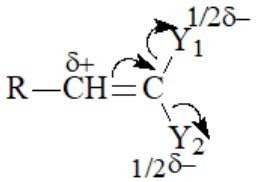
Formation of topoisomerase II inhibition complex, contributing to the chromosomal aberration *via* attack of quinone methide metabolite on the thiol functional groups of cysteine fragments in a protein (enzyme) in a similar mode as that of glutathione conjugation showed above cannot be excluded [7]:



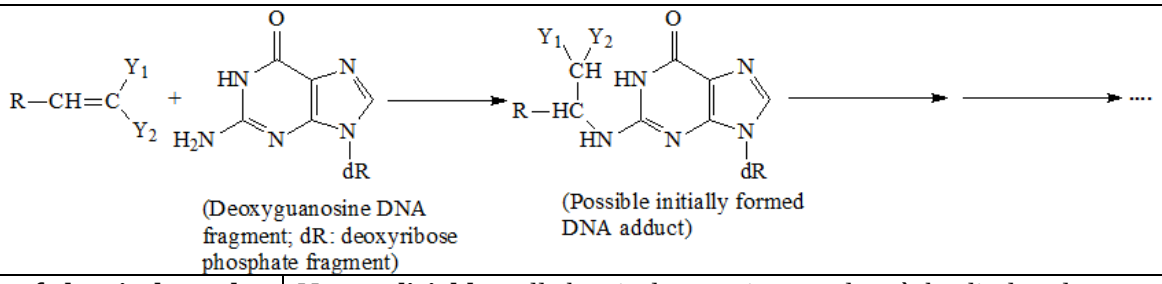
Consequently, it can be assumed that quinone methide intermediates formed during the metabolism of various chemicals can cause both the mutagenicity and chromosome aberration effects.	
Set of chemicals used for profile development	Quinone Methides
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Sweeny, Mutat. Res. **82**(2), 1981, 275 – 283. 2. Rietjens, Mutat. Res. **574** (1 – 2), 2005, 124 – 138. 3. Thompson, Chem. Res. Toxicol. **8**, 1995, 55 -60. 4. Marquest, Carcinogenesis **18**(10), 1997, 1949 – 1954. 5. Maralhasi, Mutagenesis **21**(3). 2006, 199–204. 6. Thompson, J. Biol. Chem. **264**(2), 1969, 1016 – 1021. 7. Bolton, Chem. Biol. Interact. **107**(3), 1997, 185 – 200.

Individual profile/alert	
Name	Alpha-Beta Conjugated Alkene Derivatives with Geminal Electron-Withdrawing Groups
Type of profile	Structural alert
Description/applicability domain	
Mechanism	**A_N2 Michael-type conjugate addition to activated alkene derivatives**

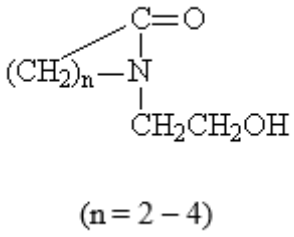
It is expertly assumed that the combination of geminally attached strong electron-withdrawing substituents (EWG) with double or triple bonds (Y1 and Y2, see above), capable of enhanced conjugation with the C=C bond gives rise to an electron deficiency at the β-carbon atom and strong electrophilicity:



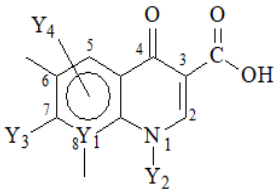
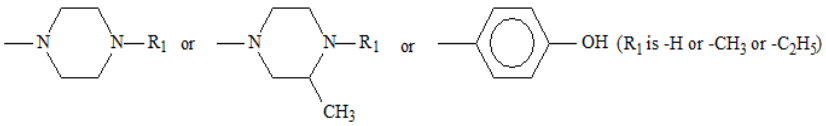
Thus some DNA alkylating capability becomes possible and it could materialize itself via mechanistic scheme, similar to Michael-type addition [4, 5], as follows:

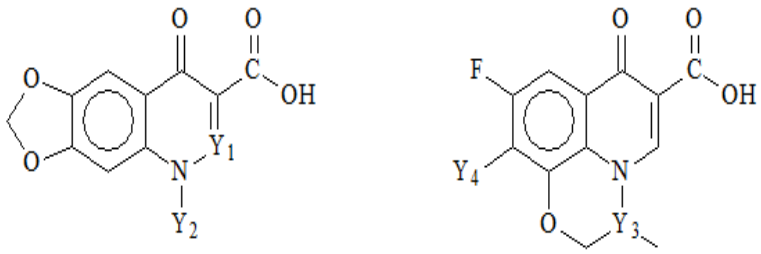


Set of chemicals used for profile development	**Not appliciable** – all chemicals are private and can`t be disclosed.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Rietveld, Mutat. Res. **188** (1987), 97 – 104. 2. *2-Propenoic Acid, 2-Cyano-, Methyl Ester (CAS 137-05-3) MSDS*; http://www.guidechem.com/msds/137-05-3.html. 3. Andersen, Mutat. Res. **102** (1982), 373 – 381. 4. Hecht, Toxicology **166** (1-2) (2001), 31 – 36. 5. Solomon, Canc. Res. **45** (1985), 3465 – 3470.

Individual profile/alert	
Name	N-Hydroxyethyl Lactams
Type of profile	Structural alert
Description/applicability domain	 (n = 2 – 4)
Mechanism	**Non-covalent interactions DNA intercalation**
Positive *in vitro* bacterial mutagenicity test results with *Salmonella typhimurium* strains TA100 and TA1535 were reported for 1-(2-Hydroxyethyl)-2-pyrrolidinone as parent chemical. The chemical is probably frameshift mutagen [1]. According to one publication, the oxopyrrolidine derivatives may interact with DNA as one of their possible mechanisms of action. For example, hydrogen bonds might be formed among the base pairs of DNA (adenine, guanine, cytosine and thymine), the free carbonyl group, and the nitrogen atom of oxopyrrolidine ring [2].	
Set of chemicals used for profile development	**Not appliciable** – all chemicals are private and can`t be disclosed.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. *2-Pyrrololidinone, 1- (2Hydroxyethyl)-, Full Public Report*, National Industrial Chemicals Notification and Assessment Scheme (NICNAS), 14 February 2005;

	https://www.nicnas.gov.au/__data/assets/word_doc/0007/18538/STD1134FR.docx, last visited 09.2019. 2. Ali, Chem. Papers **68**(4) (2014), 540 – 552. 3. Duff, J. Phys. Chem. **B 110** (2006), 20693 – 20701. 4. US Pat. 5124444 (*Lactam-Containing Compositions and Methods Useful for the Extraction of Nucleic Acids* (June 23, 1992).

Individual profile/alert	
Name	Quinolone Derivatives
Type of profile	Structural alert
Description/ applicability domain	 (Structure type 1: Fused-ring bicyclic systems) Y_1 can be C or N{V3}; Y_2 can be  or $-CH_3$ or $-CH_2CH_3$; Y_3 can be  (R_1 is -H or $-CH_3$ or $-C_2H_5$) Y_4 can be -F (positions 6 and 8) or combinations of -F (position 6) and -H (position 8) ***Notes***: 1. Positions 2 and 5 remain non-substituted; 2. If Y_1 is N{V3}, Y_3 can be *also* $-CH_3$ or $-C_2H_5$, and if Y_3 is $-CH_3$ or $-C_2H_5$ *only*, Y_4 can be -H

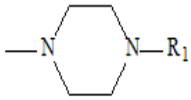
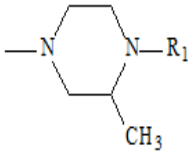


(Structures types 2 and 3: Tricyclic fused-ring systems)

Y_1 can be C or N{V3};

Y_2 can be  or $-CH_3$ or $-CH_2CH_3$;

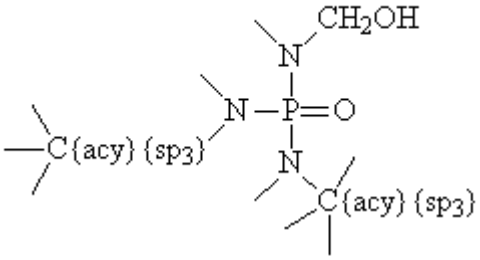
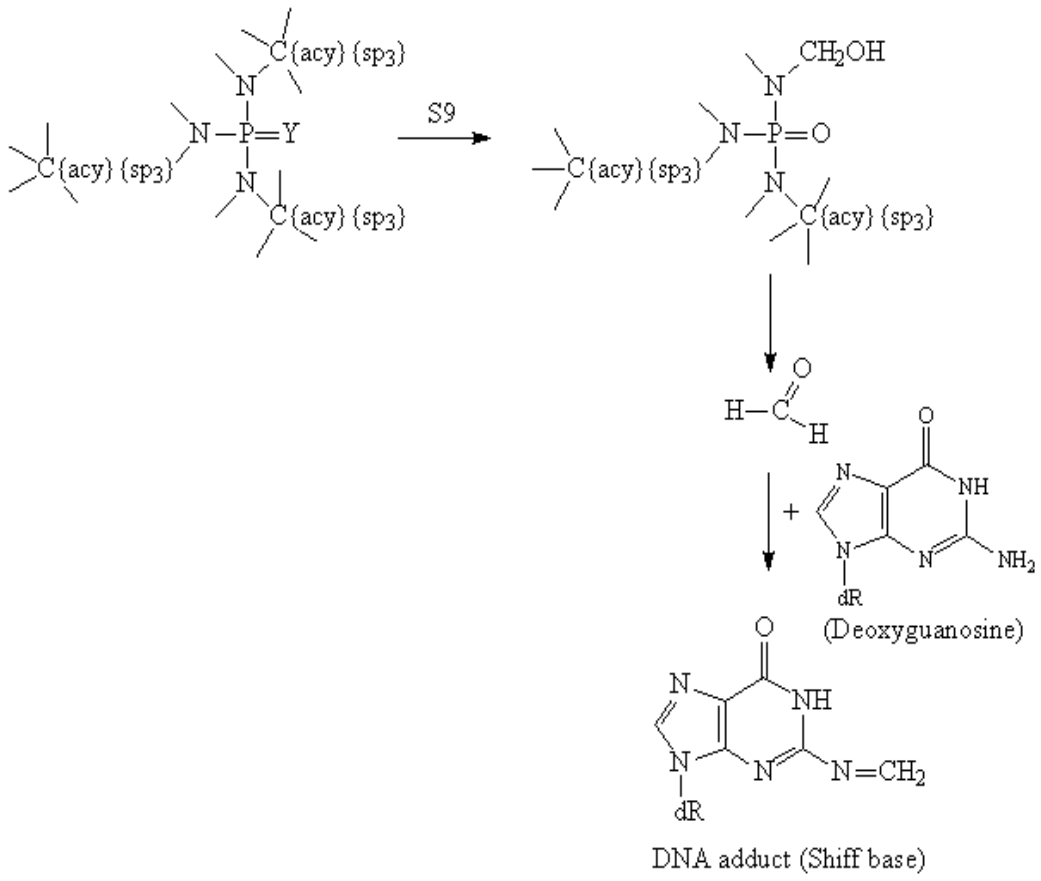
Y_3 can be CH or N{sp3}{V3}

Y_4 can be  or  (R_1 is -H or $-CH_3$ or $-C_2H_5$)

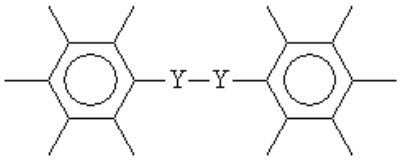
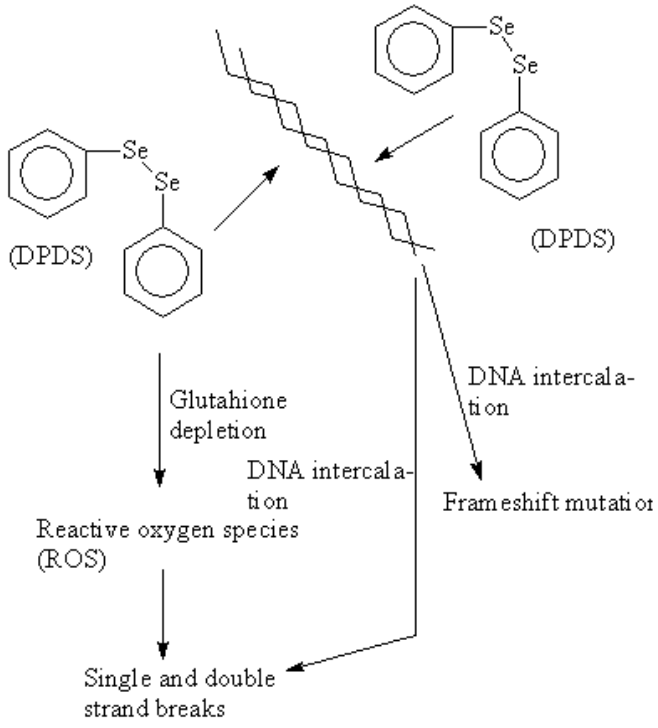
Mechanism	**Non-covalent interactions DNA intercalation**

The mechanism of genotoxicity of quinolone antibiotics involves interaction with the bacterial topoisomerase IV and DNA gyrase enzyme proteins, thereby *indirectly* causing DNA degradation and mutation. These chemicals induce the gyrase enzyme to cleave the DNA with protein covalently bound at the site-specific double-strand scission. The chemicals are highly specific for the bacterial gyrase enzyme, and their bacterial mutagenicity cannot be extended and generalized to mammalian cells. Thus the term “genotoxic” means an increase of the occurrence of DNA lesions by various complex mechanisms, not involving *direct* DNA reactivity [4].

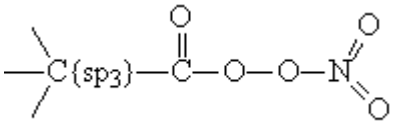
Set of chemicals used for profile development	Quinolone Derivatives
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Kirkland, D., *Mutat. Res.* **2005**, 584(1 -2), 1 – 256. 2. Albertini, S., *Mutagen*. **1995**, 10(4), 343 – 351. 3. Mamber, S.W., *Antimicrob. Agents Chemother*. **1993**, 37(2), 213 – 217. 4. Gocke, E., Mutat. Res. **1991**, 248(1), 135 – 143. 5. Vashist, J., *Ind. J. Biochem. & Biophys*. **2009**, 147 – 153. 6. Heddle, J., *Antimicrob. Agents and Chemother*. **2002**, 46(6), 1805 – 1815. 7. Peterson, L. R., *Clin. Infect. Diseases*, **2001**, 33(Suppl. 3), S180 – S186.

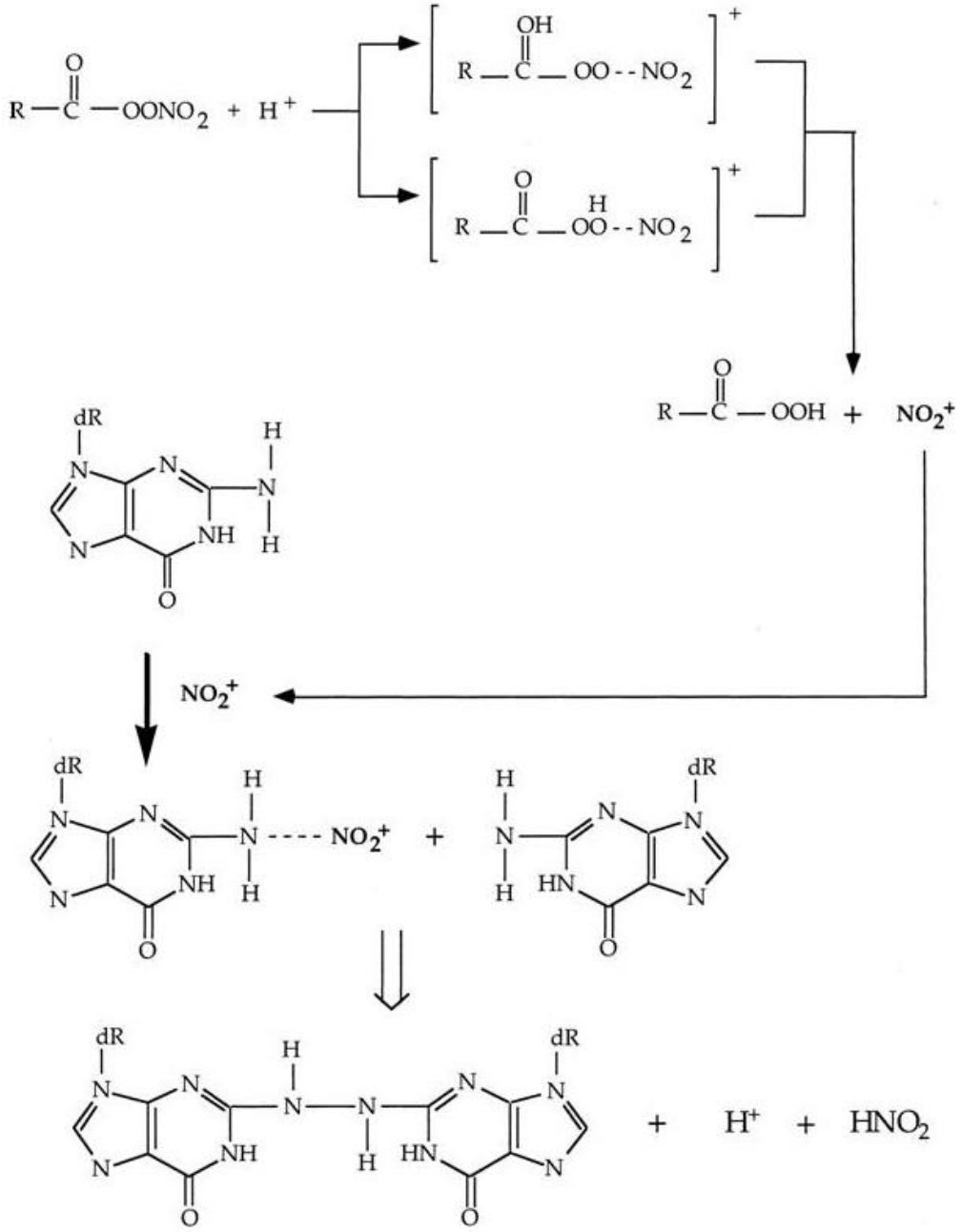
Individual profile/alert	
Name	Non-Cyclic Alkyl Phosphoramides and Thionophosphoramides
Type of profile	Structural alert
Description/applicability domain	 C(acy) (sp3) corresponds to -CH_3 or -C_2H_5 or -CH_2OH; no more than two -CH_2OH groups, should be bound to different N-atoms)
Mechanism	**A_N2 Shiff base formation (after S9 metabolic activation only)**
 DNA adduct (Shiff base)	
Set of chemicals used for profile development	Non-Cyclic Alkyl Phosphoramides and Thionophosphoramides
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Anderson, D., Br. J. Cancer, **37**(6) (**1**978**)**, 924 – 930.

	2. Sarrif, A.M., Mutat. Res., **380**(1-2) **(**1997), 167 - 177. 3. CCRIS: Hexamethylphosphoramide, Toxicology Data Network, U.S. National Library of Medicine; http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+ccris:@term+@rn+680-31-9. 4. Jones, A. R., Biochem. Pharmacol. **17** (1968), 2247 – 2252. 5. Ashby, J., Br. J. Cancer **38** (1978), 418 – 429. 6. Lu, K., J. Am. Chem. Soc. **132**(10) (2010), 3388 – 3399.

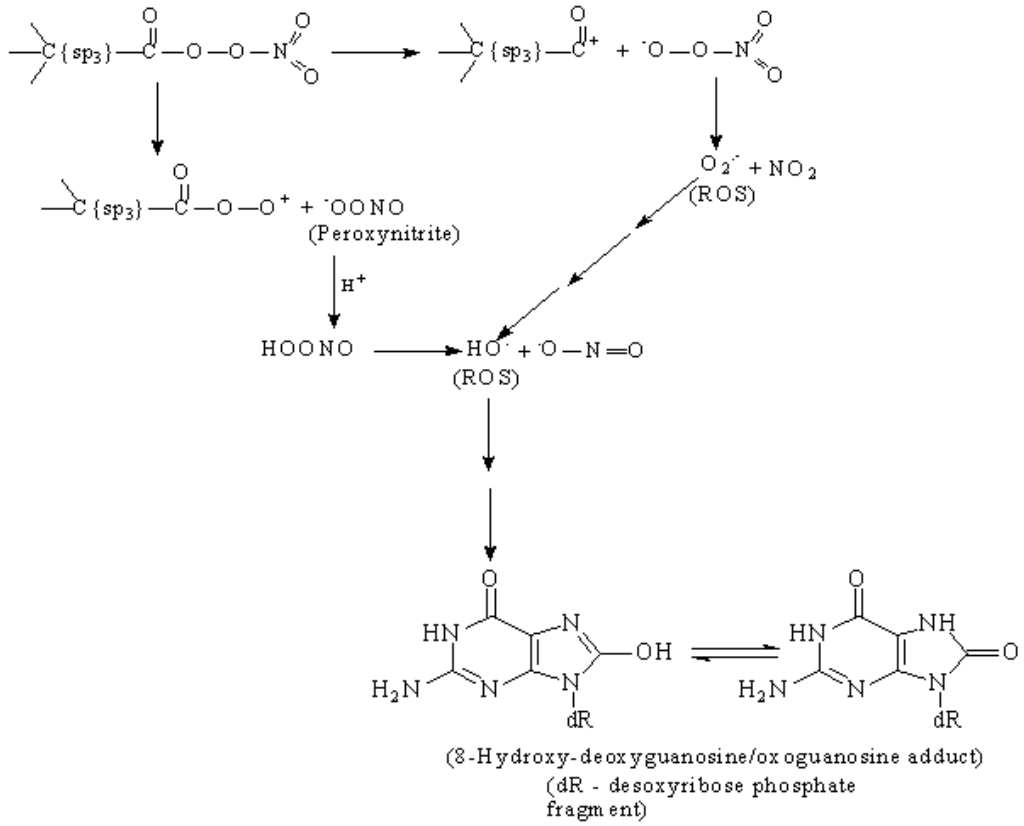
Individual profile/alert	
Name	Organic Diselenides and Ditellurides
Type of profile	Structural alert
Description/applicability domain	 (Y is Se or Te)
Mechanism	**Non-covalent interactions DNA intercalation and Radical ROS generation**
	
Set of chemicals used for profile development	Organic Diselenides and Ditellurides
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded

	in this profiler according to the references listed below.
References	1. Rosa, Mutat. Res. 563(2) (2004**)**, 107 - 115. 2. Degrandi, Mutagen. **25**(3) (2010), 257 – 269. 3. Rosa, Braz. J. Med. Biol. Research **40** (2007), 1287 – 1304. 4. Brito, Acta Biochim. Pol. **56**(1) (2009), 125 – 134. 5. Prigol, Chem. Biol. Interact. **200** (2012) 65 – 72.

Individual profile/alert	
Name	Peroxyacyl Nitrates
Type of profile	Structural alert
Description/applicability domain	
Mechanism	**Radical ROS generation and S_N1 or S_N2 Nitrosation**
The following mechanistic scheme for the generation of active electrophilic species and interaction with DNA (deoxyguanosine fragment) has been suggested [3]:	

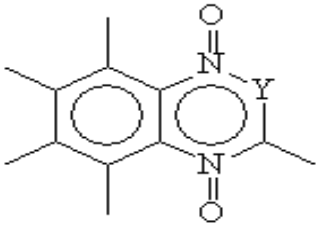


According to another mechanistic hypothesis, PAN may release peroxyacetyl nitrite and other reactive oxygen species (ROS) such as superoxide, hydrogen peroxide and hydroxide radical, which may cause mutagenicity and cell apoptosis. The corresponding scheme of ROS generation and formation of DNA adduct can be outlined as follows [5]:

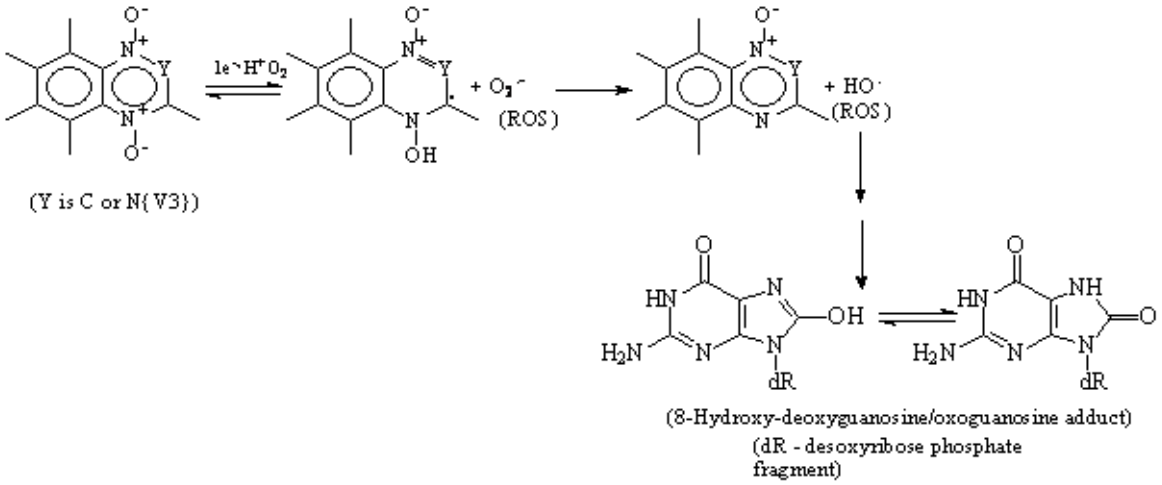


Set of chemicals used for profile development	Peroxyacyl Nitrates
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Kleindienst, Mutat. Res. **157**(2-3) (1985), 123 - 128. 2. Kleindienst, Environ. Mol. Mutagen. **16**(2) (1990), 70 - 80. 3. DeMarini, Mutat. Res. **457**(1-2) (2000**)**, 41 – 55. 4. CCRIS: *Peroxyacetylnitrate, Toxicology Data Network*, U.S. National Library of Medicine**;** http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+ccris:@term+@rn+2278-22-0. 5. Liu, Mol. Carcinog. **25** (1999), 196 – 206.

Individual profile/alert	
Name	Quinoxaline-Type 1,4-Dioxides
Type of profile	Structural alert

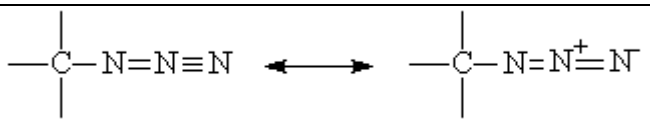
Description/applicability domain	 (Y is C or N{V3})
Mechanism	**Radical ROS generation**

The following scheme for generation of ROS and formation of DNA adducts can be assumed [5]:

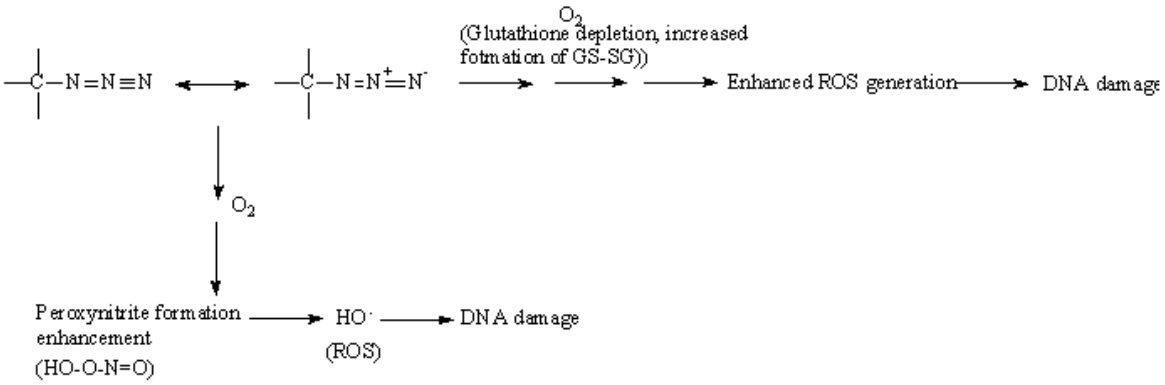


Set of chemicals used for profile development	Quinoxaline-Type 1,4-Dioxides
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Yoshimura, Mutat. Res.90(1) (1981**)**, 49 – 55. 2. Nunoshiba, Mutat. Res. **217**(3) (1989**)**, 203 - 209. 3. Beutin, Antimicrob. Agents Chemother.20(3) (1981**),** 336 - 343. 4. Voogd, Mutat. Res. 78 (1980) 233 – 242. 5. Ganley, Bioorg. & Med. Chem. **9** (2001), 2395 – 2401. 6. Liu, Toxicol. Lett. **195** (2010), 51 - 59.

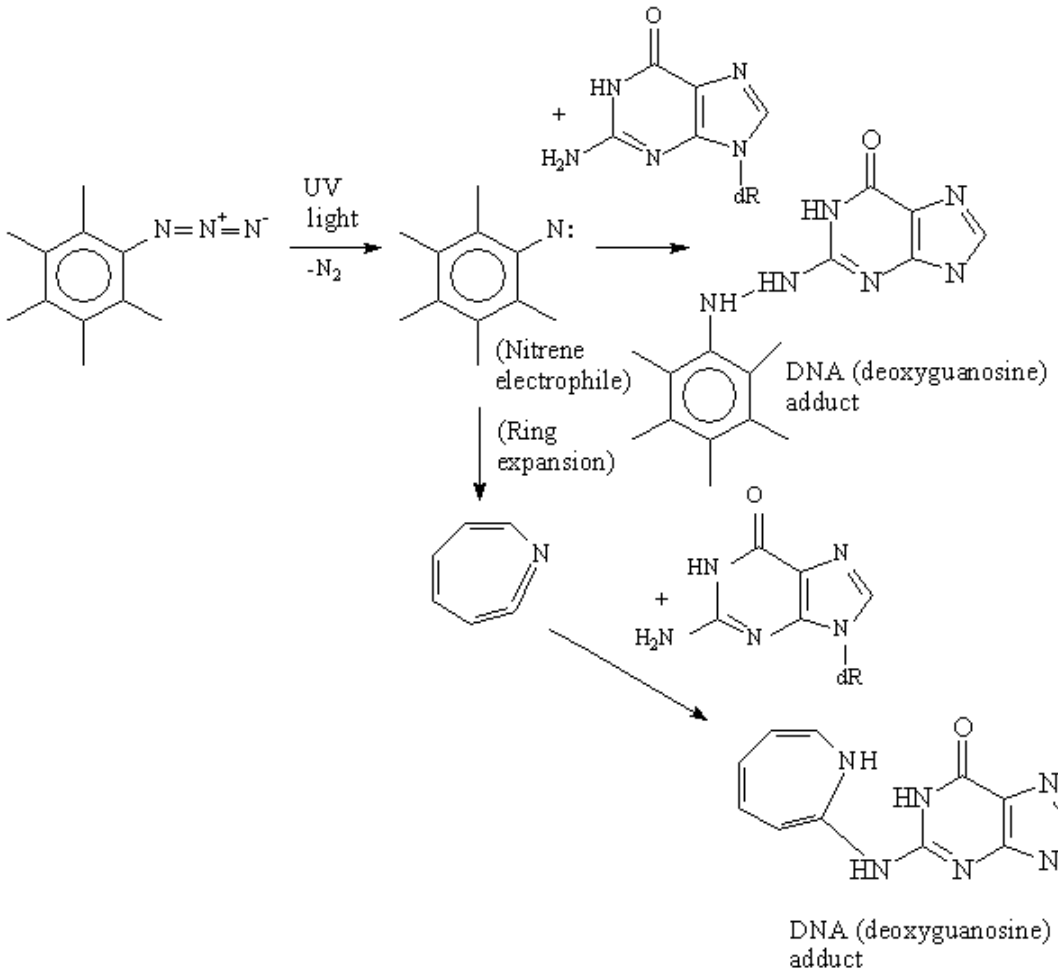
Individual profile/alert	
Name	Organic Azides
Type of profile	Structural alert

Description/applicability domain	
Mechanism	**Radical ROS generation, S_N1 Nucleophilic attack after nitrene formation and Non-covalent interactions DNA intercalation**

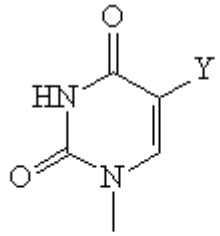
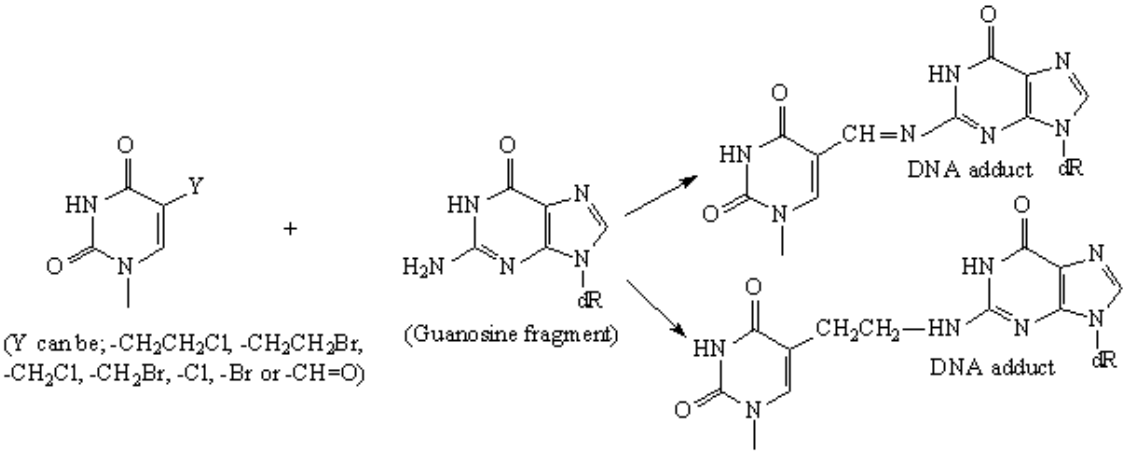
Two principal mechanisms of DNA damage, eliciting bacterial mutagenicity can be suggested. The first one is associated with the pro-oxidant properties of organic azides such as AZT, resulting in endogenous glutathione depletion and enhanced peroxynitrite and reactive oxygen species (ROS) formation [9, 10]. The following mechanistic scheme can be expertly outlined:

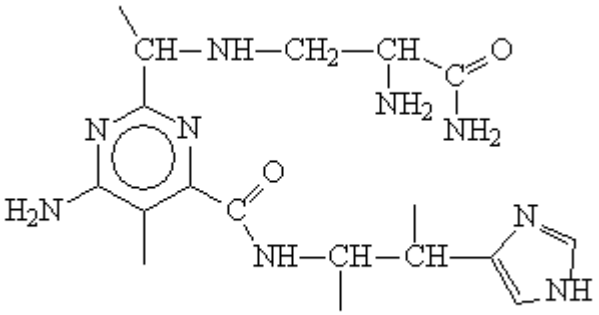
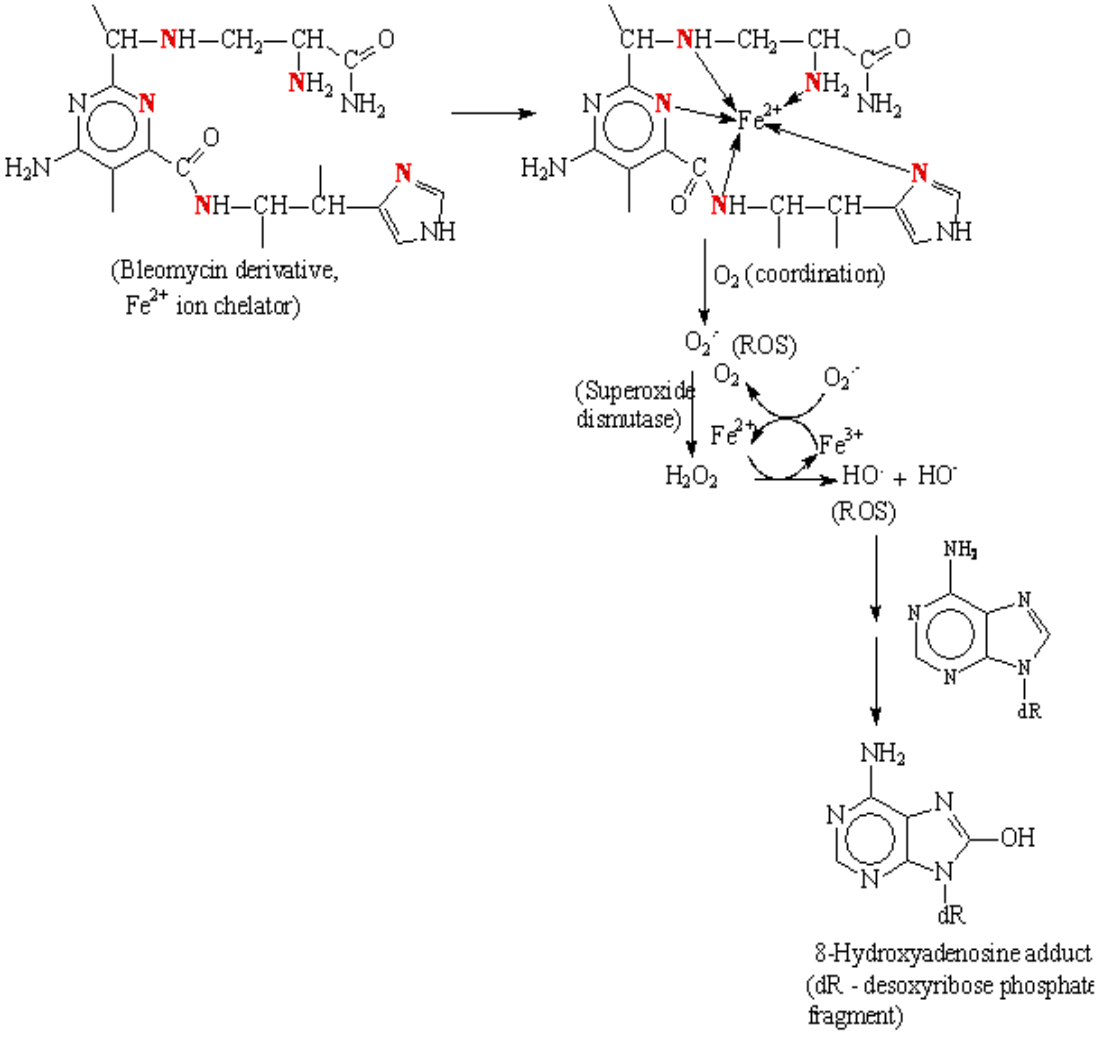


The second mechanism is mainly associated with arylazides, and the subsequent generation of electrophilic arylnitrene species, following light activation [11]. The following expertly assumed mechanistic scheme can be outlined:

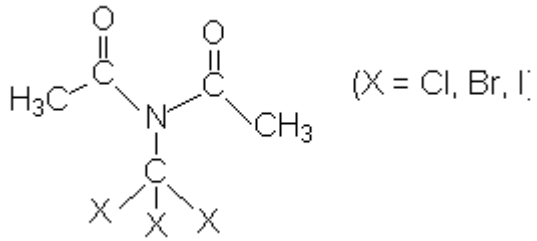
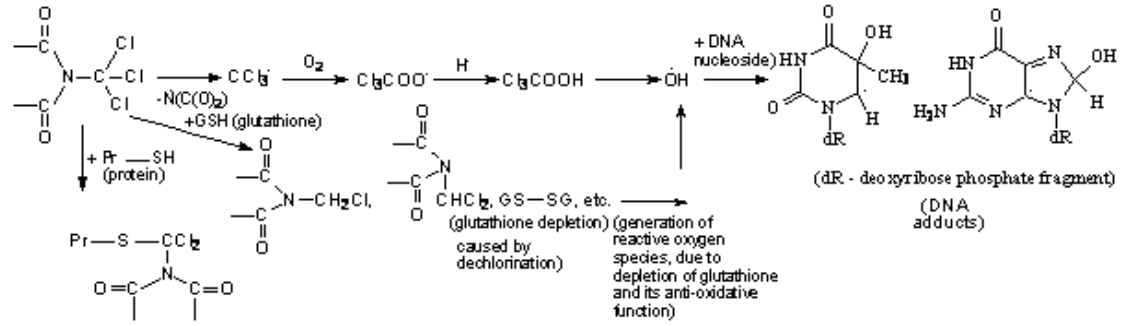


Set of chemicals used for profile development	Organic Azides
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Zeller, Toxicol. Sci. **135**(2) (2013**)**, 317 - 327. 2. Ayers, Fundam. Appl. Toxicol. **32**(2) (1996), 148 - 158. 3. Ballardin, Ann. N.Y. Acad. Sci. **1056** (2005**)**, 303 - 310. 4. Gao, Mol. Med. Report **4**(1) (2011), 151 – 155. 5. Bialkowska, Carcinog. **21**(5) (2000), 1059 – 1062. 6. Olivero, Environ. Molec. Mutagen. **48** (2007), 215 – 223. 7. Owais, Mutat. Res. **118** (1983), 229 – 239. 8. Owais, Mutat. Res. **197** (1988), 313 – 323. 9. Osborne, J. AIDS Clin. Res. 6(4) (2015); DOI: 10.4172/2155-6113.1000441. 10. Mak, Cardiovasc. Toxicol**. 04** (2004), 109 – 115). 11. Photoreactive Crosslinker Chemistry, Transfection & Genome Engineering Handbook; http://www.lifetechnologies.com/bg/en/home/life-science/protein-biology/protein-biology-learning-center/protein-biology-resource-library/pierce-protein-methods/photoreactive-crosslinker-chemistry.html#, last visited 09.2019.

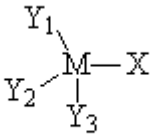
Individual profile/alert	
Name	Specific 5-Substituted Uracil Derivatives
Type of profile	Structural alert
Description/applicability domain	 (Y can be; -CH_2CH_2Cl, -CH_2CH_2Br, -CH_2Cl, -CH_2Br, -Cl, -Br or -CH=O)
Mechanism	**A_N2 Shiff base formation, S_N2 Alkylation, nucleophilic substitution at sp3-carbon atom and Non-covalent interactions DNA intercalation**
Formation of covalent adducts, DNA or DNA/protein cross-linking – schemes of formation of some possible DNA adducts are given below:  (Y can be; -CH_2CH_2Cl, -CH_2CH_2Br, -CH_2Cl, -CH_2Br, -Cl, -Br or -CH=O) (Guanosine fragment) DNA adduct DNA adduct	
Set of chemicals used for profile development	Specific 5-Substituted Uracil Derivatives
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Suter, Mutat. Res. **568**(2) (**2004**), 195 - 209. 2. Szinai, Eur. J. Drug Metabol. Pharmacokinet. **16**(2) (1991), 129 – 136. 3. Privat, Mutat. Res. **354** (1996), 151 – 156.

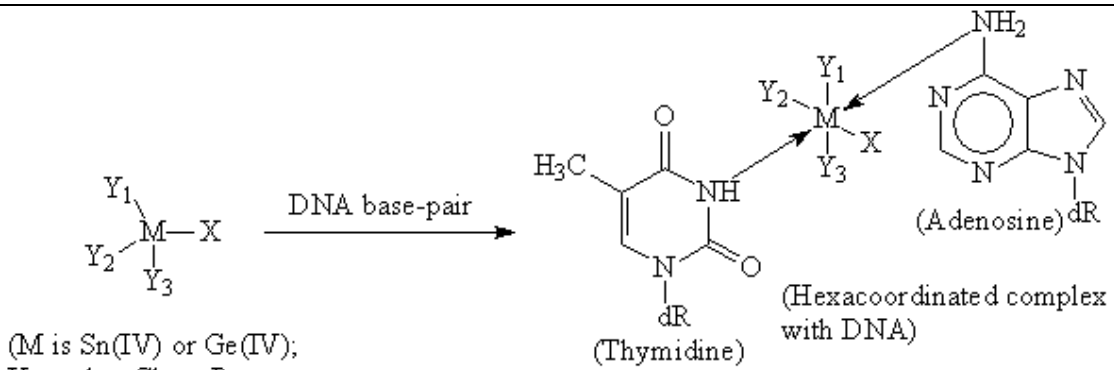
Individual profile/alert	
Name	Bleomycin and Structurally Related Compounds
Type of profile	Structural alert
Description/applicability domain	
Mechanism	**Radical ROS generation & Non-covalent interactions DNA intercalation**
	
Set of chemicals used for profile development	Bleomycin and Structurally Related Compounds

Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Anderson, D., Mutat. Res. **329**(1) (1995**)**, 37 - 47. 2. Tom, W. M., Biochem. Pharmacol. **29** (1980), 3239 – 3244. 3. Lazo, J. St., Proc. Natl. Acad. Sci. USA **80** (1983), 3064 – 3068. 4. Yamanaka, N., Canc. Res. **38** (1978), 3900 – 3903. 5. Tuimala, J., Carcinog. **23**(6) (2002), 1003 – 1008. 6. Oppenheimer, N. J., Proc. Natl. Acad. Sci. USA **76**(11) (1979), 5616 – 5620. 7. Chapter 2, Literature Review I. Bleomycin 2.1. Chemistry of Bleomycin, University of Pretoria; http://repository.up.ac.za/bitstream/handle/2263/24472/02chapter2.pdf?sequence=3). 8. Podger, D. M., Mutat. Res. **117** (1983), 9 – 19. 9. Dixon, Sc. J., Nature Chemical Biology **10** (2014), 9 – 17.

Individual profile/alert	
Name	N-Trihalomethyldiacylimides
Type of profile	Structural alert
Description/applicability domain	
Mechanism	**Acylation Direct acylation involving a leaving group**
	
Set of chemicals used for profile development	**Not Appliciable**
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Schneider, M., G. B. Quistad, J. E. Casida, *Glutathione Activation of Chloropicrin in the Salmonella Mutagenicity Test*, Mutat. Res. **439**(2), 1999, 233 – 238.

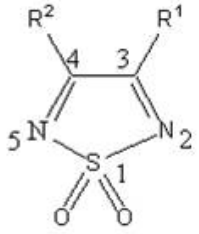
	2. Sparks, S. E., G. B. Quistad, J. E. Casida, *Chloropicrin: Reactions with Biological Thiols and Metabolism in Mice*, Chem. Res. Toxicol. **10**(9), 1997, 1001 – 1007. 3. IPCS Inchem Home, FAO Meeting Report No. PL/1965/10/2, *Evaluation of the Hazards to Consumers Resulting from the Use of Fumigants in the Protection of Food*, WHO/Food Add/28.65, Food and Agriculture Organization of the United Nations, World Health Organization, 1965 http://www.inchem.org/documents/jmpr/jmpmono/v65apr05.htm 4. Toxicological Review of Carbon Tetrachloride (CAS No. 56-23-5), In Support of Summary Information on the Integrated Risk Information System (IRIS), March 2010, US-EPA, Washington DC; http://www.epa.gov/iris/toxreviews/0020tr.pdf 5. Kovacic, P., J. D. Jacintho, *Mechanisms of Carcinogenesis: Focus on Oxidative Stress and Electron Transfer*, Current Medic. Chem. **8**, 2001, pp. 773 – 796. 6. Witherell, H. L., R. A. Hiatt, M. Replogle, J. Parsonnet, *Helicobacter pylori Infection and Urinary Excretion of 8-Hydroxy-2-Deoxyguanosine, an Oxidative DNA Adduct*, Canc. Epidemiol. Biomarkers & Prevention **7** (1998), 91 – 96. 7. Wiseman, H., B. Halliwell, *Damage to DNA by Reactive Oxygen and Nitrogen Species: Role in Inflammatory Disease and Progression to Cancer*, Biochem. J. 313 (1996), 17 – 29.

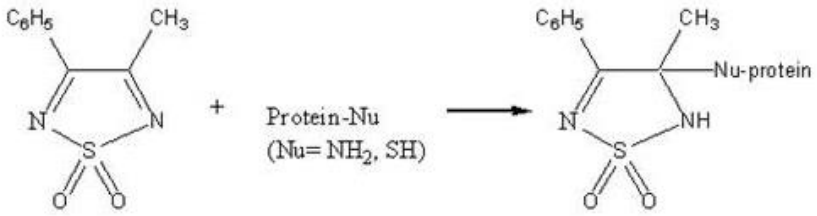
Individual profile/alert	
Name	Short-Chain Alkytin and Alkylgermanium Halides
Type of profile	Structural alert
Description/applicability domain	 (M is Sn(IV) or Ge(IV); X can be -Cl or -Br; Y_1, Y_2 can be -Cl or -Br or $-(CH_2)_nH$ (n = 1 - 4) Y_3 can be $-(CH_2)_nH$ (n = 1 - 4))
Mechanism	**S_N2 Coordination with nucleoside bases**



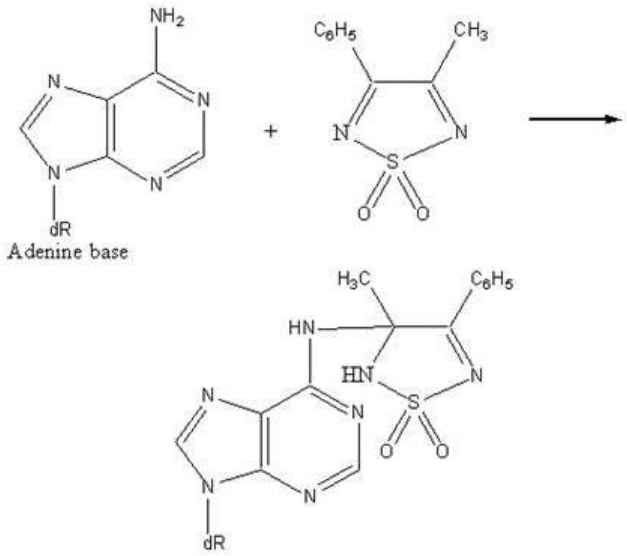
(M is Sn(IV) or Ge(IV);
X can be -Cl or -Br;
Y_1, Y_2 can be -Cl or -Br or $-(CH_2)_nH$ (n = 1 - 4)
Y_3 can be $-(CH_2)_nH$ (n = 1 - 4))

Set of chemicals used for profile development	Short-Chain Alkyltin and Alkylgermanium Halides
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Hamasaki, TMutat. Res., 300(3-4) (1993**)**, 265 - 271. 2. Li, Toxicol. Appl. Pharmacol. **64** (1982), 482 – 485. 3. Shoukry, The Scientific World Journal, (**2013**), 1 – 7. 4. Rastogi, J. Appl. Chem. (**2014**), 1 – 5.

Individual profile/alert	
Name	Thiadiazoledioxide Derivatives
Type of profile	Structural alert
Description/applicability domain	 Where R^1 and R^2 are Hydrogen, Alkyl or Aryl
Mechanism	**1,2,5-Thiadiazole 1,1-dioxide derivatives**
It was found that 3-methyl-4-phenyl-1,2,5-thiadiazole 1,1-dioxide was a moderate skin sensitizer [5]. The mechanism of interaction with skin proteins is presented below:	

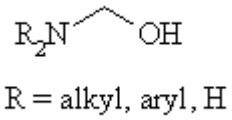
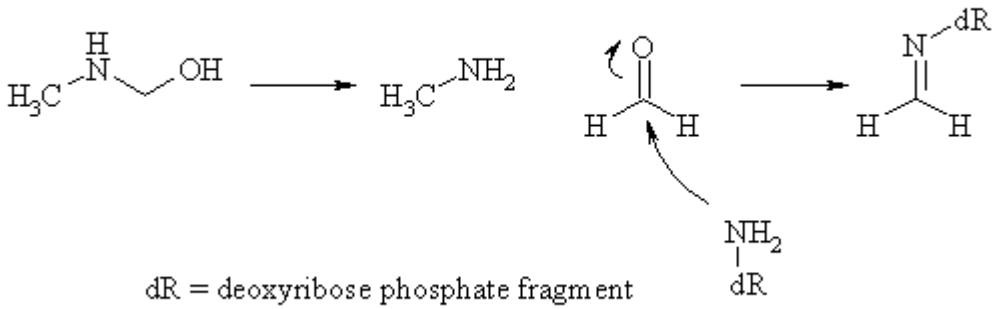


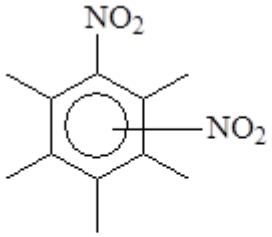
It may be assumed that thiadiazole dioxide derivatives can bind to the amino groups in DNA bases regardless of their lower nucleophility.



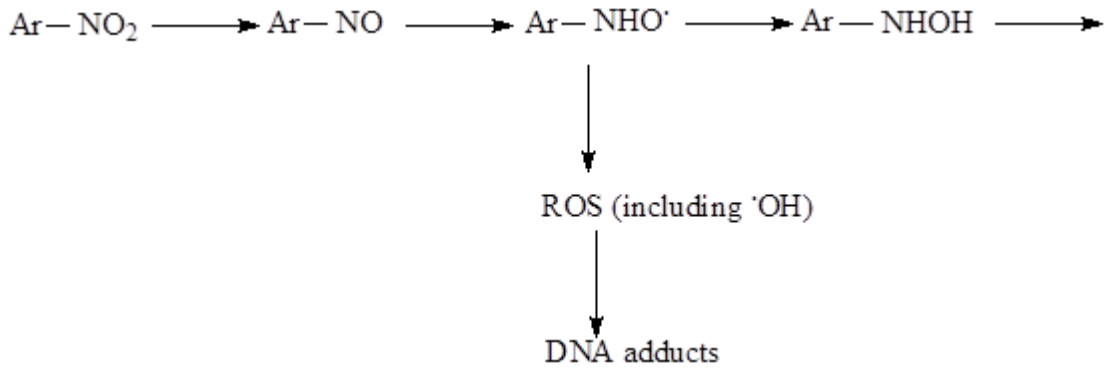
Set of chemicals used for profile development	**Not Appliciable**
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below..
References	1. J. A. Caram, can. J. Chem. 1996, 74(8), 1564-1571. 2. V. J. Aran, Adv. Heterocycl. Chem. 1988, Vol.44, 81-197 3. R. Y. Wen, J. Org. Chem. 1975, Vol.40(19), 2743-2746. 4. J. A. J. Phys. Org. Chem. 2003, 16(4), 220-225. 5. G. Patlewicz, Chem. Res. Toxicol. 2008, 21(2), 521-541.

Individual profile/alert	
Name	N-Methylol Derivatives
Type of profile	Structural alert

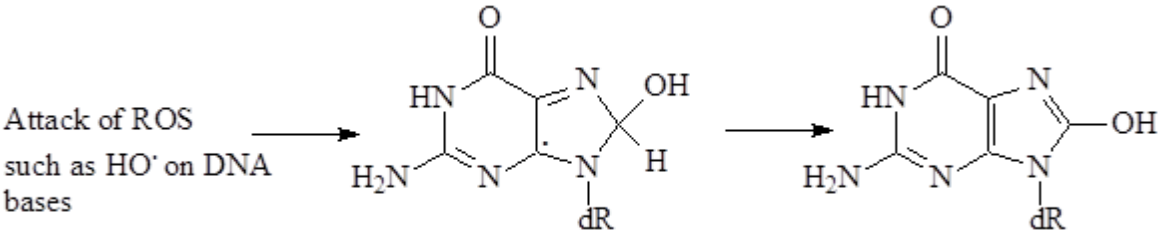
Description/applicability domain	
Mechanism	**Schiff base formation Chemicals Activated by P450 to Mono-aldehydes**
N-methylol derivatives have been suggested to be genotoxic via hydrolysis into formaldehyde (Ashby et al 1985). Formaldehyde then undergoes DNA binding via a Schiff base reaction (Cheng et al 2003). 	
Set of chemicals used for profile development	N-methylol derivatives
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Ashby et al (1985) Mutation Research, 156, 19-32 2. Cheng et al (2003) Chemical Research in Toxicology, 16, 145-152

Individual profile/alert	
Name	Polynitroarenes
Type of profile	Structural alert
Description/applicability domain	 (Single arene ring in the whole molecular structure only; number of -NO_2 groups 2 or 3; number of substituents: no more than 4)
Mechanism	**SN1: Nucleophilic attack after reduction and nitrenium ion formation and radical: ROS generation**
Radical (Homolytic) Mechanism**.** This is one of the mechanisms (*but not the most important*) for eliciting bacterial mutagenicity of nitro compounds. Certain monocyclic and polycyclic aromatic nitro compounds ($ArNO_2$) are implicated in carcinogenesis [5]. Reduction of the nitro to the nitroso	

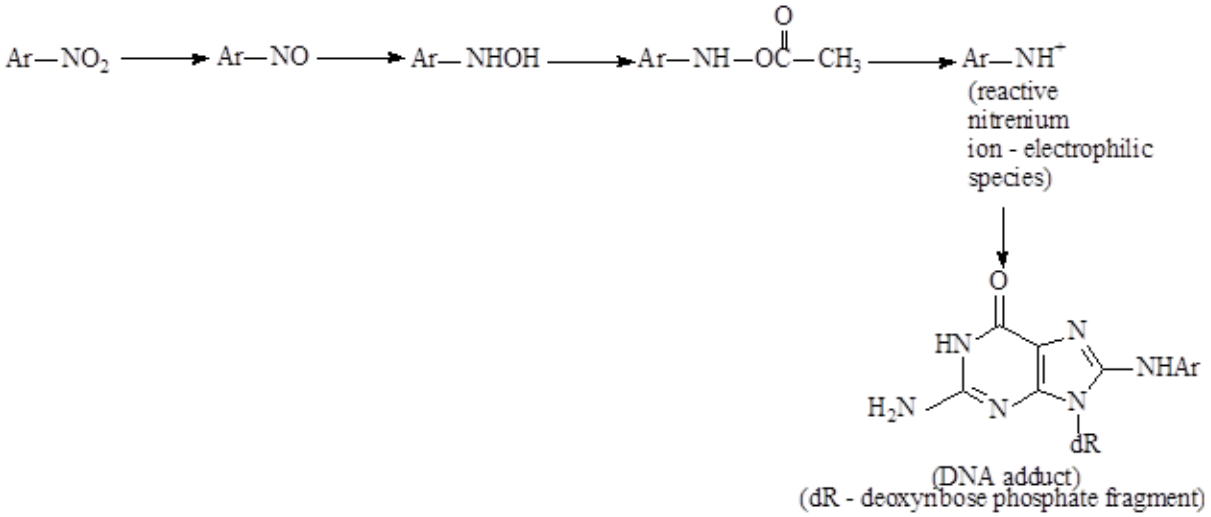
intemediate is followed by formation of N-hydroxylamine species and may occur in the prokaryotic *Salmonella typhimurium* cell. Several transient *radical intermediates*, including reactive oxygen species (ROS) are formed during this process, and have been found to cause oxidative DNA damage (strand breaks)**:**



As a result from the generation of reactive radical species such as ArNHO·, an additional formation of ROS such as $O_2^{\cdot -}$ and/or HO· occurs. The hydroxyl radical, for example, is DNA-reactive and adducts, involving pyrimidine and purine nucleoside bases can be formed. The 8-hydroxyguanine adduct is one of the most mutagenic lesions so far discovered, which can induce DNA strands breaks, etc. [6, 7]:



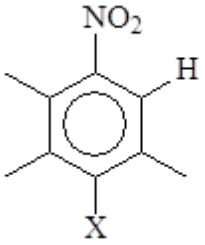
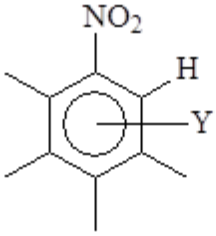
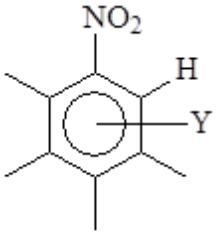
Heterolytic Mechanism. This is the most important mechanism, associated with the bacterial mutagenicity of nitroarenes, and, particularly, the sub-class discussed here. The DNA damage, eliciting bacterial mutagenicity results mainly from covalent adduct formation. It arises from several activated metabolites, including the N-hydroxylamine (proximate mutagenic form) and its O-esterified derivative formed by phase II (O-acetylation, sulfation) enzymatic reaction with the subsequent generation of electrophilic nitrenium ion. The latter species may exert electrophilic attack on DNA bases [1, 2, 8]:



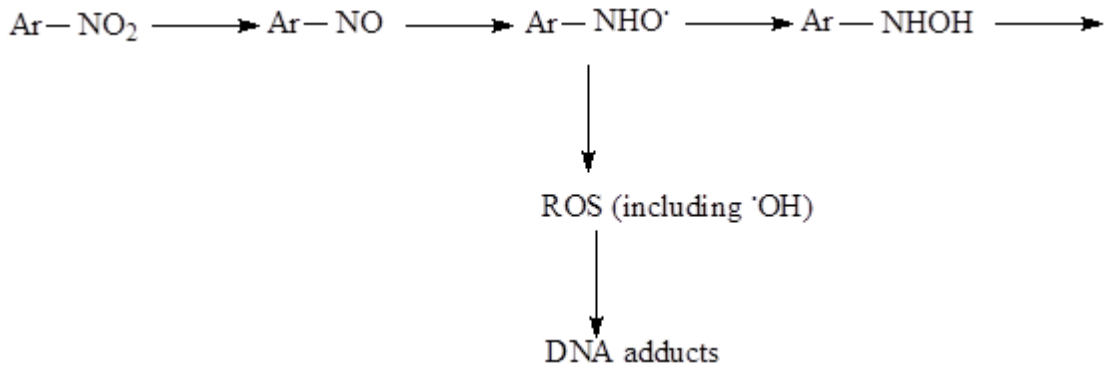
Chemicals such as 2,6-dinitrotoluene, 2,4-dinitrotoluene, 2,4,6-trinitrotoluene, etc., containing more

than one nitro group were found to be bacterial mutagens both in the presence and the absence of S9 mix [4].	
Set of chemicals used for profile development	Polynitroarenes
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Sabbioni, G., Hemoglobin Binding of Arylamines and Nitroarenes: Molecular Dosimetry and Quantitative Structure-Activity Relationships, Envir. Health Persp. 102, Suppl. 6 (1994), 61 – 67. 2. Kalgutkar, A. S., I. Gardner, R. S. Obach, C. L. Shaffer, E. Callegari, K. R. Henne, A. E. Mutlib, D. K. Dalvie, J. S. Lee, Y. Nakai, J. P. O, Donnell, J. Boer, S. P. Harriman, A Comprehensive Listing of Bioactivation Pathways of Organic Functional Groups, Current Drug Metabol. 6 (2005), 161 – 225. 3. Aiub, Cl. A. Fortes, J. L. Mazzei, L. F. R. Pinto, I. Felzenszwalb, Evaluation of Nitroreductase and Acetyltransferase Participation in N-Nitrosodiethylamine Genotoxicity, Chem.-Biol. Interact. 161 (2006), 146 – 154. 4. Einisto, P., M. Watanabe, M. Ishidate Jr., T. Nohmi, Mutagenicity of 30 Chemicals in Salmonella typhimurium Strains Possessing Different Nitroreductase or O-Acetyltransferase Activities, Mutat. Res. 259 (1991), 95 – 102. 5. Kovacic, P., J. D. Jacintho, Mechanisms of Carcinogenesis: Focus on Oxidative Stress and Electron Transfer, Current Med. Chem. 8, (2001), 773 – 796. 6. Witherell, H. L., R. A. Hiatt, M. Replogle, J. Parsonnet, Helicobacter pylori Infection and Urinary Excretion of 8-Hydroxy-2-deoxyguanosine, an Oxidative DNA Adduct, Canc. Epidemiol. Biomarkers & Prevention 7 (1998), 91 – 96. 7. Wiseman, H., B. Halliwell, Damage to DNA by Reactive Oxygen and Nitrogen Species: Role in Inflammatory Disease and Progression to Cancer, Biochem. J. 313 (1996), 17 – 29. 8. Purohit, V., A. K. Basu, Mutagenicity of Nitroaromatic Compounds, Chem. Res. Toxicol. 13(8) (2000), 673 – 692. 9. Grummt, T., H. G. Wunderlich, A. Chakraborty, M. Kundi, B. Majer, Fr. Ferk, A. K. Nersesyan, W. Parzefall, S. Knasmuller, Genotoxicity of Nitrosulfonic Acids, Nitrobenzoic Acids and Nitrobenzylalcohols, Pollutants Commonly Found in Ground Water Near Ammunition Facilities, Environ. Molec. Mutag. 47 (2006), 95 – 106.

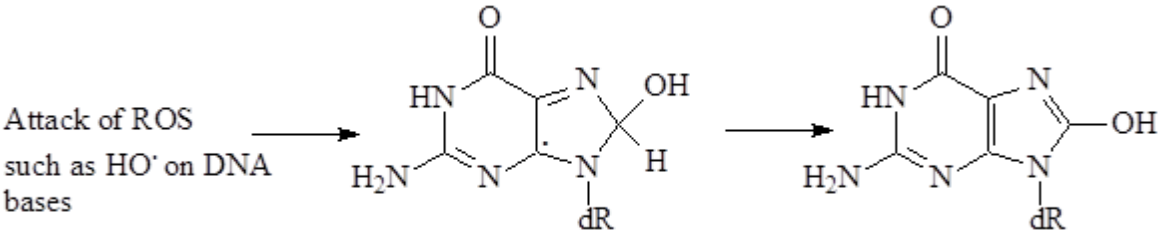
Individual profile/alert	
Name	Nitroarenes with Other Active Groups
Type of profile	Structural alert
Description/applicability	

domain	**Halonitroarenes:**  (X can be -F, -Cl, -Br, -I; totally no more that four substituents) **Nitrobenzyl and Nitrobenzoyl Halides:**  (Y can be $-CH_2X$ (X is -Cl, -Br, -F, -I) or —C(=O)X; totally, no more than four substituents) **Nitrophenyl Diazonium Salts and Nitrophenyl Triazenes:**  (Y can be $-N=N-N\{V_3\}\{sp_3\}$(triazene) or $-N^{+}\equiv N$ (diazonium)); totally no more than four substituents)
Mechanism	A. For the nitro group function: S_N1: Nucleophilic attack after reduction and nitrenium ion formation and Radical: ROS generation (indirect) B. For the alternative active functionalities: S_N2 or S_N1: Nucleophilic attack after diazonium or carbenium ion formation; S_N2 attack on activated carbon Csp3 or Csp2
Radical (Homolytic) Mechanism**.** This is one of the mechanisms (*but not the most important*)	

for eliciting bacterial mutagenicity of nitro compounds. Certain monocyclic and polycyclic aromatic nitro compounds ($ArNO_2$) are implicated in carcinogenesis [5]. Reduction of the nitro to the nitroso intemediate is followed by formation of N-hydroxylamine species and may occur in the prokaryotic *Salmonella typhimurium* cell. Several transient *radical intermediates*, including reactive oxygen species (ROS) are formed during this process, and have been found to cause oxidative DNA damage (strand breaks)**:**

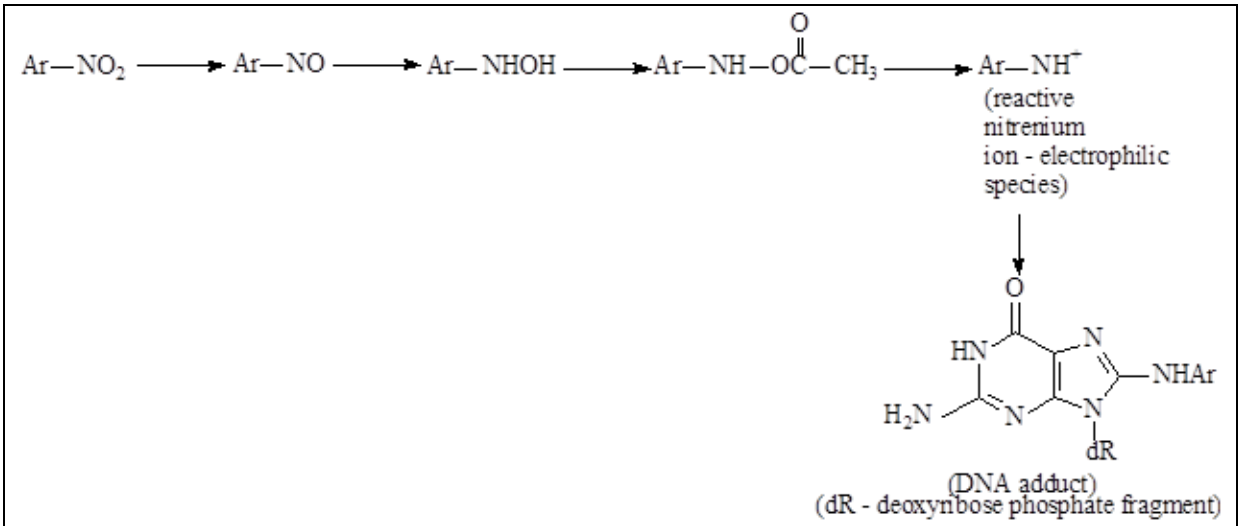


As a result from the generation of reactive radical species such as $ArNHO^{\cdot}$, an additional formation of ROS such as $O_2^{\cdot-}$ and/or $HO^{\cdot}$ occurs. The hydroxyl radical, for example, is DNA-reactive and adducts, involving pyrimidine and purine nucleoside bases can be formed. The 8-hydroxyguanine adduct is one of the most mutagenic lesions so far discovered, which can induce DNA strands breaks, etc. [6, 7]:



(dR - deoxyribose phosphate fragment) (Deoxyguanosine adduct)

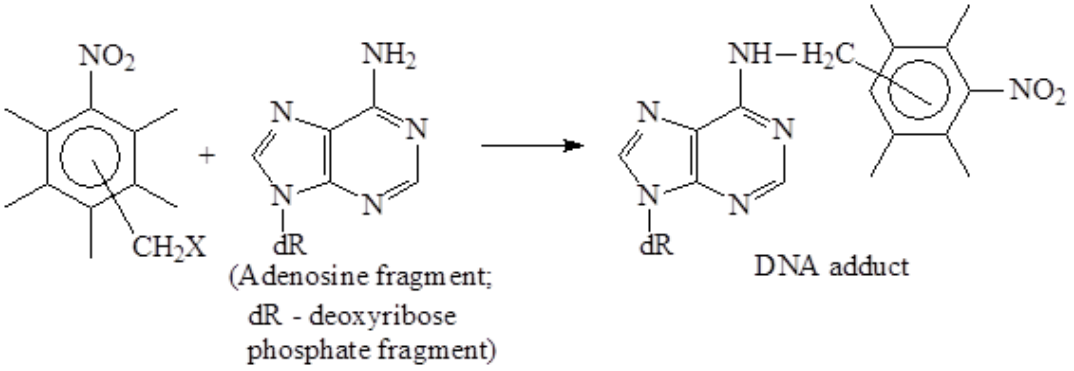
Heterolytic Mechanism. This is the most important mechanism, associated with the bacterial mutagenicity of nitroarenes, and, particularly, the sub-class discussed here. The DNA damage, eliciting bacterial mutagenicity results mainly from covalent adduct formation. It arises from several activated metabolites, including the N-hydroxylamine (proximate mutagenic form) and its O-esterified derivative formed by phase II (O-acetylation, sulfation) enzymatic reaction with the subsequent generation of electrophilic nitrenium ion. The latter species may exert electrophilic attack on DNA bases [1, 2, 8]:



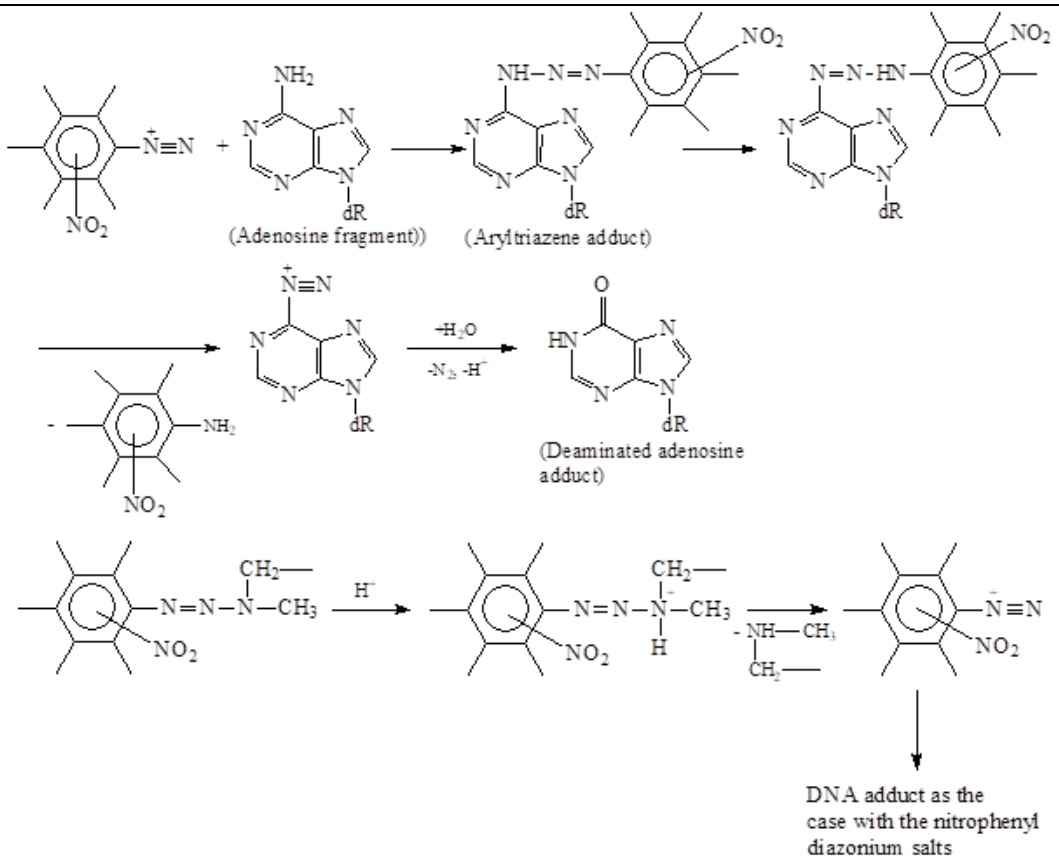
Among the isomers of chloronitrobenzenes, only *p*-chloronitrobenzene (4-chloronitrobenzene) showed mutagenicity in *Salmonella typhimurium* when tested in the presence or absence of induced rodent liver S9 [9]. This confirms the importance of *p*-position with respect to the nitro group in eliciting direct mutagenicity through stabilization of electrophilic carbenium ions in the resonance structures, and reduced steric hindrance [10, 11].

Additional chemical mechanistic schemes, other than those associated with nitro group reduction to N-hydroxylamine or generation of ROS (see above) are associated with some nitroarenes, containing other active functionalities and belonging to other classes of *Ames*-positive chemicals involved in the direct mutagenicity effects. Such schemes are outlined below:

For nitrobenzyl and nitrobenzoyl halides – aralkylation [13]:

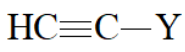


For nitrophenyl diazonium salts and triazenes [14, 15]:



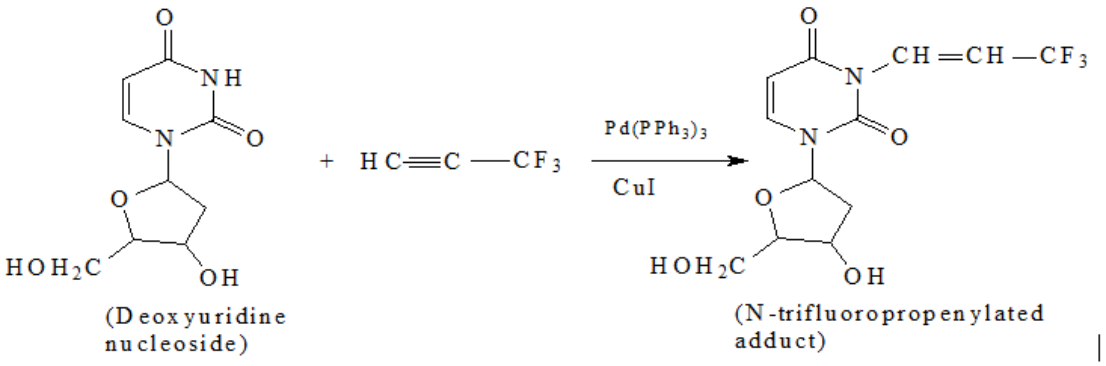
Set of chemicals used for profile development	Nitroarenes with Other Active Groups
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Sabbioni, G., Hemoglobin Binding of Arylamines and Nitroarenes: Molecular Dosimetry and Quantitative Structure-Activity Relationships, Envir. Health Persp. 102, Suppl. 6 (1994), 61 – 67. 2. Kalgutkar, A. S., I. Gardner, R. S. Obach, C. L. Shaffer, E. Callegari, K. R. Henne, A. E. Mutlib, D. K. Dalvie, J. S. Lee, Y. Nakai, J. P. O, Donnell, J. Boer, S. P. Harriman, A Comprehensive Listing of Bioactivation Pathways of Organic Functional Groups, Current Drug Metabol. 6 (2005), 161 – 225. 3. Aiub, Cl. A. Fortes, J. L. Mazzei, L. F. R. Pinto, I. Felzenszwalb, Evaluation of Nitroreductase and Acetyltransferase Participation in N-Nitrosodiethylamine Genotoxicity, Chem.-Biol. Interact. 161 (2006), 146 – 154. 4. Einisto, P., M. Watanabe, M. Ishidate Jr., T. Nohmi, Mutagenicity of 30 Chemicals in Salmonella typhimurium Strains Possessing Different Nitroreductase or O-Acetyltransferase Activities, Mutat. Res. 259 (1991), 95 – 102. 5. Kovacic, P., J. D. Jacintho, Mechanisms of Carcinogenesis: Focus on Oxidative Stress and Electron Transfer, Current Med. Chem. 8, (2001), 773 – 796.

	6. Witherell, H. L., R. A. Hiatt, M. Replogle, J. Parsonnet, Helicobacter pylori Infection and Urinary Excretion of 8-Hydroxy-2-deoxyguanosine, an Oxidative DNA Adduct, Canc. Epidemiol. Biomarkers & Prevention 7 (1998), 91 – 96. 7. Wiseman, H., B. Halliwell, Damage to DNA by Reactive Oxygen and Nitrogen Species: Role in Inflammatory Disease and Progression to Cancer, Biochem. J. 313 (1996), 17 – 29. 8. Purohit, V., A. K. Basu, Mutagenicity of Nitroaromatic Compounds, Chem. Res. Toxicol. 13(8) (2000), 673 – 692. 9. 2-Chloronitrobenzene, 3-Chloronitrobenzene and 4-Chloronitrobenzene, IARC Monographs Vol. 65 (1997); http://monographs.iarc.fr/ENG/Monographs/vol65/volume65.pdf. ISBN-13 (PDF): 978-92-832-1565-3. 10. Shimizu, M., E. Yano, Mutagenicity of Mono-Nitrobenzene Derivatives in the Ames Test and Rec Assay, Mutat. Res. 170 (1986), 11 – 22. 11. Chemical Carcinogenesis Research Information System, TOXNET, US National Library of Medicine; http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?CCRIS, last visited 09.2019. 12. Hemminki, K., K. Falck, K. Linnainmaa, Reactivity, SCE Induction and Mutagenicity of Benzyl Chloride Derivatives, J. Appl. Toxicol. 3(4) (1983), 203 – 207. 13. Fall, M., H. Haddouk, J. P. Morin, R. Forster, Mutagenicity of Benzyl Chloride in the Salmomella/Microsome Mutagenesis Assay Depends on Exposure Conditions, Mutat. Res. 633(1) (2007), 13 – 20; http://www.ncbi.nlm.nih.gov/pubmed/17631040. DOI: 10.1016/j.mrgentox.2007.04.017. 14. Lawson, T., P. M. Gannett, W. M. Yau, N. S. Dalal, B. Toth, Different Patterns of Mutagenicity of Arenediazonium Ions in V79 Cells and Salmonella typhimurium TA102: Evidence for Different Mechanisms of Action, J. Agric. Food Chem. 43 (1995), 2627 – 2635. 15. Marchesi, Fr., M. Turriziani, Gr. Tortorelli, G. Avvisati, Fr. Torino, L. De Vecchis, Triazene Compounds: Mechanism of Action and Related DNA Repair Systems, Pharmacol. Res. 56 (2007), 275 – 287.

Individual profile/alert	
Name	Propyne Derivatives – Potential DNA Reactivity
Type of profile	Structural alert
Description/applicability domain	 (Y are electron-withdrawing groups such as $-CF_3$, $-CHF_2$, $-CH_2F$, $-CH_2Cl$, $-CH_2Br$ or –CH=O)

Mechanism	SN_2: Alkylation, nucleophilic substitution at sp3-carbon atom AN_2: Nucleophilic addition to α,β-unsaturated carbonyl compounds

The reaction of 3,3,3-trifluoropropyne (CAS No. 661-54-1) with 2'-deoxyuridine to give N-propenylated nucleoside (N3-alkylation) was reported to occur, according to the following scheme:

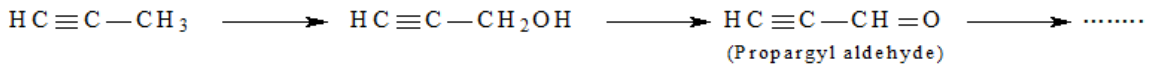


(Scheme 1)

In some separate experiments, however, it was shown that the catalyst was not required for the adduct formation. The mechanism of N-trifluoropropenylation was considered to be similar to the Michael-type addition. Here the N3 atom of pyrimidine fragment adds as a nucleophile to the terminal carbon atom of trifluoropropyne, which is electrophilic, due to the presence of strong electron-withdrawing –CF3 group (Scheme 1) [1]:

Therefore, despite the lack of relevant data on the in vitro genotoxicity of trihalopropynes such as 3,3,3-trifluoropropyne, potential DNA reactivity of this chemical is assumed.

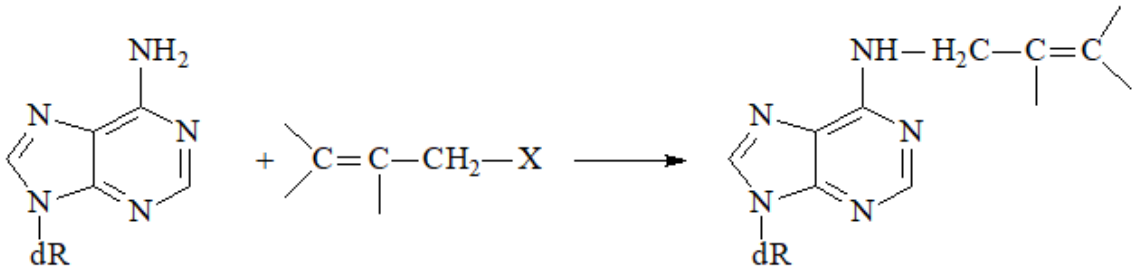
After microsomal/S9 metabolic activation, propyne may be converted into propargyl aldehyde by the following scheme:



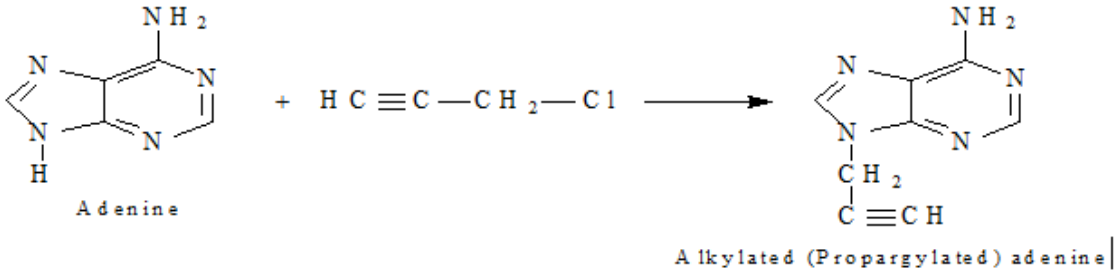
(Scheme 2)

Propargyl aldehyde has been reported to be strong bacterial mutagen [2]. It is likely to exert its DNA reactivity by a mechanism, similar to that depicted in Scheme 1 above.

Structurally close chemicals with electron-withdrawing -CH2Br or -CH2Cl groups attached to -C#CH fragment such as propargyl chloride and propargyl bromide, and positive bacterial mutagenicity data were found by read-across analysis. However, these chemicals are assumed to be DNA-reactive by different (SN) mechanism of DNA-alkylation (via heterolytic cleavage of the labile C-Hal bond), similarly to their allylic-type analogues (Schemes 3 and 4) [3, 4]:



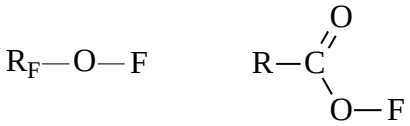
(Scheme 3)



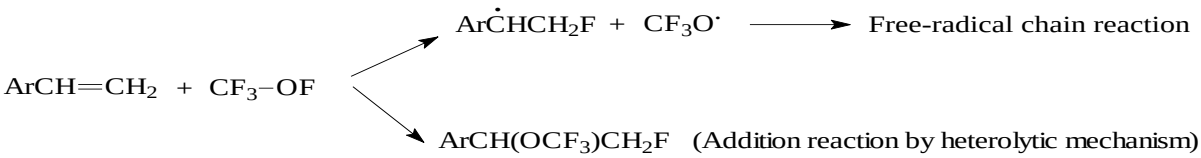
(Scheme 4)

Conclusion: Chemicals from the sub-class discussed above are assumed to be DNA-reactive and are likely to exert positive in vitro genotoxicity effects.

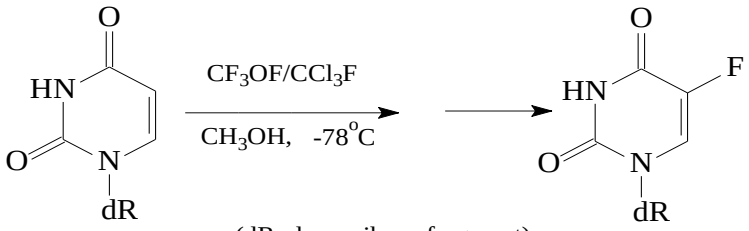
Set of chemicals used for profile development	Propyne Derivatives
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Chirakul, P., S. Th. Sigurdsson, Unexpected Formation of 2'-Deoxy-N3-(3,3,3-Trifluoro-1-Propenyl) Uridine via a Michael-Type Addition to 3,3,3-Trifluoropropyne, Tetrahed. Lett. 44 (2003), 6899 – 6901. 2. Basu, A. K., L. J. Marnett, Molecular Requirements for the Mutagenicity of Malondialdehyde and Related Acroleins, Canc. Res. 44 (1984), 2848 – 2854. 3. Eder, E., D. Henschler, T. Neudecker, Mutagenic Properties of Allylic and Alpha,beta-Unsaturated Compounds: Consideration of Alkylating Mechanisms Xenobiotica 12(12), 1982, 831-848. 4. Joshy, R. V., J. Zemlicka, Alkylation of Adenine with t-Propargyl Chlorides: Acetylene/Allene Ratio and N9/N1 Regioselectivity, Tetrahedron, 49 (12) (1993), 2353 – 2360.

Individual profile/alert	
Name	Perfluorinated Hypofluorites – Potential DNA Reactivity
Type of profile	Structural alert
Description/applicability domain	 (R_F is C_nF_{2n+1} (perfluorinated alkyl chain); R is C_nH_{2n+1} or C_nF_{2n+1}, n = 1 - 5)
Mechanism	S_E2: Electrophilic substitution at sp3 and sp2-carbon atoms A_E2: Electrophilc addition to C=C double bond

The following generalized mechanistic scheme involving radical and/or heterolytic mechanism of interactions of perfluoroalkyl hypofluorites with alkenes has been assumed [2]:



Direct fluorination of uracil and cytosine bases and nucleosides by using trifluoromethyl hypofluorite has been reported. The formation of DNA fluorinated adduct(s) would occur, according to the following general scheme [3]:

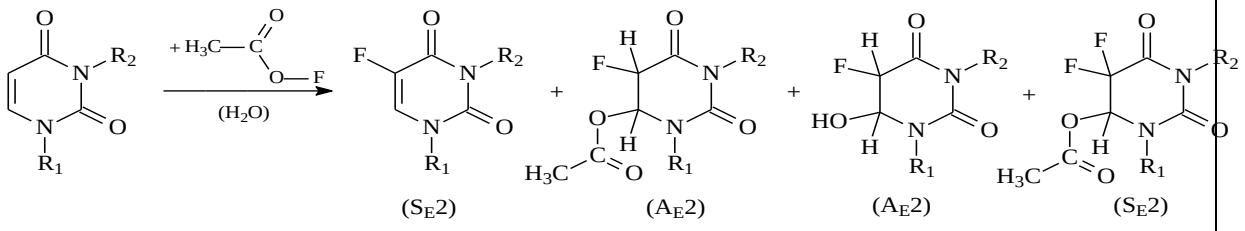


(dR: deoxyribose fragment)

(Scheme 1)

The reaction of acetyl hypofluorite with DNA bases such as uracil, cytosine and some of their N-substituted derivatives dissolved in water has been studied. Cytosine adducts readily underwent deamination in water to the corresponding uracil analogues. The following schemes for interaction, occurring by electrophilc attacks of fluorine on DNA bases have been suggested [5]:

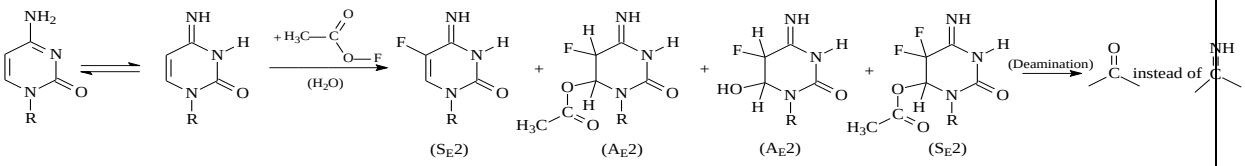
<u>Uracil and Its Derivatives (Scheme 2):</u>



(R_1, R_2 are H (both) or -CH_3 (both) or H and -CH_3)

(Scheme 2)

Cytosine and Its Derivatives (Scheme 3):

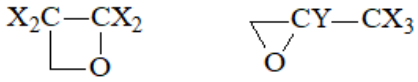


(R is H or -CH_3)

(Scheme 3)

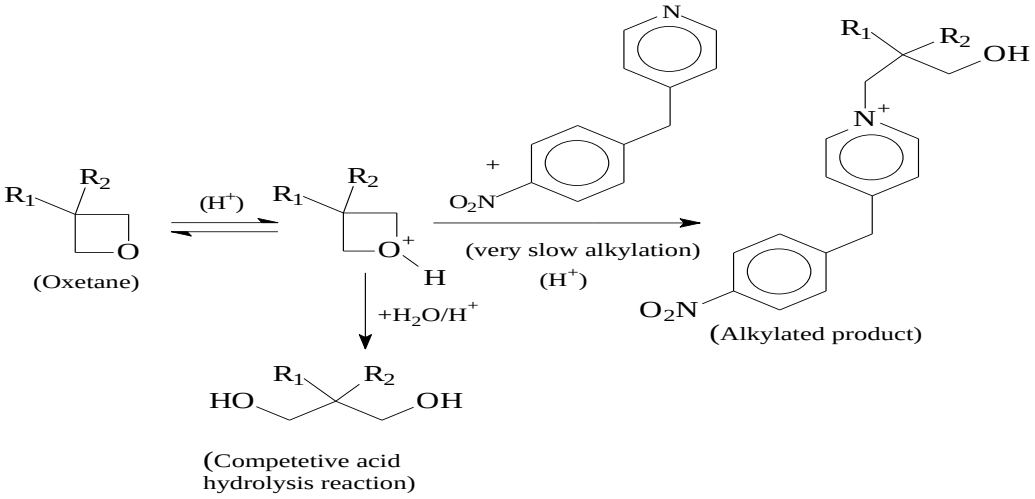
Conclusion: Chemicals from the sub-class discussed above are assumed to be DNA-reactive and, despite of lack of any relevant data, are likely to exert positive in vitro genotoxicity effects.

Set of chemicals used for profile development	Perfluorinated Hypofluorites
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Navarrini, W., FR. Venturini, M. Sansotera, M. Ursini, P. Metrangolo, G. Resnati, M. Galimberti, E. Barchiei, P. Dardani, The use of perfluoroalkyl hypofluorites for an efficient synthesis of perfluorinated ethers characterized by low Ostwald coefficient, J. Fluor. Chem. 129 (2008), 680 – 685. 2. Navarini, W., V. Tortelli, A. Russo, S. Corti, Organic Hypofluorites and Their New Role in Industrial Fluorine Chemistry, J. Fluor. Chem. 95 (1999), 27 – 39. 3. Robins, M. J., M. MacCoss, S. R. Naik, G. Ramani, Nucleic Acid Related Compounds. 21. Direct Fluorination of Uracil and Cytosine Bases and Nucleosides Using Trifluoromethyl Hypofluorite. Mechanism, Stereochemistry, and Synthetic Applications, J. Am. Chem. Soc. 98:23 (1976), 7381 – 7389. 4. Acetyl Hypofluorite; http://reag.paperplane.io/00000028.htm, last visited 09.2019.. 5. Visser, G. W. M., R. E. Herder, F. J. J. deKanter, D. M. Jacobus, Fluorination of Pyrimidines. Part 2. Mechanistic Aspects of the Reaction of Acetyl Hypofluorite with Uracil and Cytosine Derivatives, J. Chem. Soc. Perkin Trans. I, 1988, 1203 – 1207.

Individual profile/alert	
Name	Halogenated Oxetanes and Haloepoxides: DNA Reactivity
Type of profile	Structural alert
Description/applicability domain	 (X is F or Cl; Y is F, Cl or CH_3)
Mechanism	S_N2: Alkylation, direct acting epoxides and related

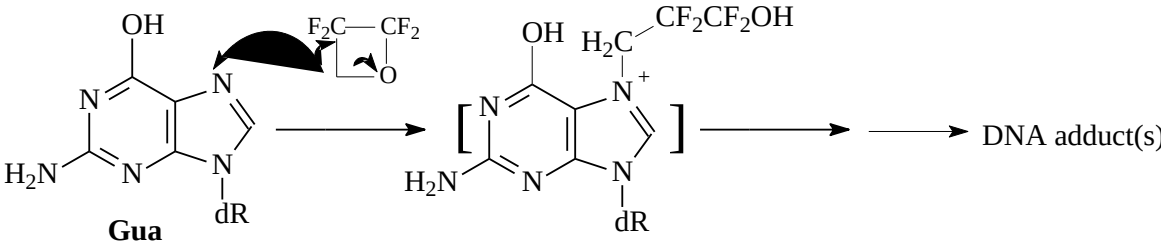
I. Halogenated Oxetanes

Alkylation of the model compound 4-(p-nitrobenzyl)pyridine (NDP) with hydrocarbon-type (non-fluorine-containing) oxetanes occurs very slowly under acidic conditions as illustrated by the following scheme:



(Scheme 1)

Introduction of electron-withdrawing fluorine (or, possibly, chlorine) atoms bound to the cyclic carbons would enhance the elctrophilicity, and the ring-opening DNA alkylating capacity of the partially fluorinated oxetanes by heterolytic cleavage of the CH_2-O bond (Scheme 2):



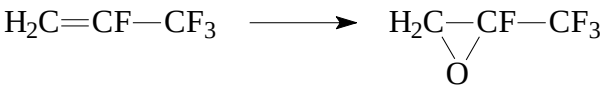
(dR - deoxyribose phosphate fragment;
Gua: Guanine nucleosides)

(Scheme 2)

II. Haloepoxides

The chemical 2,3,3,3-tetrafluoropropene (HFO-1234yf) was reported positive in the bacterial

mutagenicity test with Salmonella typhimurium strain TA100 and E. coli (WP2 uvrA) with metabolic activation only [4]. On the other hand, the biotransformation studies showed the epoxide (Scheme 3) as the primary active metabolite of HFO-1234yf [5] (Scheme 3):



2,3,3,3-Tetrafluoropropene (HFO-1234yf)

2,3,3,3-Tetrafluoropropene epoxide (active metabolite)

(Scheme 3)

Set of chemicals used for profile development	Halogenated Oxetanes and Haloepoxides
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with DNA binding to be defined and encoded in this profiler according to the references listed below.
References	1. Bombarelli, R. G., B. Br. Palma, C. Martins, M. Kranendonk, A. C. Rodriges, E. Calle, J. Rueff, J. Casado, Alkylating Potential of Oxetanes, Chem. Res. Toxicol. 23 (2010), 1275 – 1281) 2. 2,2,3,3-Tetrafluorooxetane, CAS No 765-63-9. ECHA Legal Notice, Registration Dossier. https://echa.europa.eu/de/registration-dossier/-/registered-dossier/6126/7/7/2); 3. List of Mutagenic Substances, Japan National Center for Occupational Safety and Health; https://www.jniosh.johas.go.jp/icpro/jicosh-old/english/topics/mutagenicchemicals/mutagenicchemicals.html). 4. Tveit, A., G. M. Rusch, H. Muijser, M. M. Tegelenbosch-Shouten, The Acute, Developmental, Genetic and Inhalation Toxicology of 2,3,3,3-tetrafluoropropene (HFO-1234yf), Drug Chem. Toxicol. 36(4) (2013), 412 – 420. 5. T. Schmidt, Biotransformation of trans-1-Chloro-3,3,3-Trifluoropropene and 2,3,3,3-Tetrafluoropropene, Dissertation zur Erlangung des Naturwissenschaftlichen Doktorgrades der Julius-Maximilians-Universitat Wurzburg, Bad Kissingen, Wurzburg, 2013. 6. Wade, D.R., Airy, S.C., Sinsheimer, J.E., Mutagenicity of aliphatic epoxides. Mutat. Res. 58(2-3) (1978), 217 - 223.