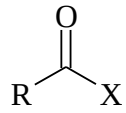
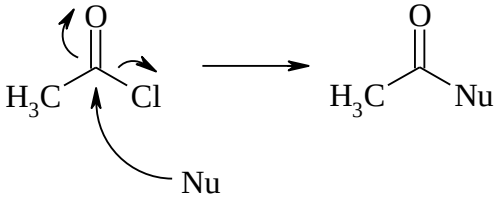
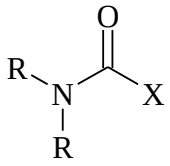
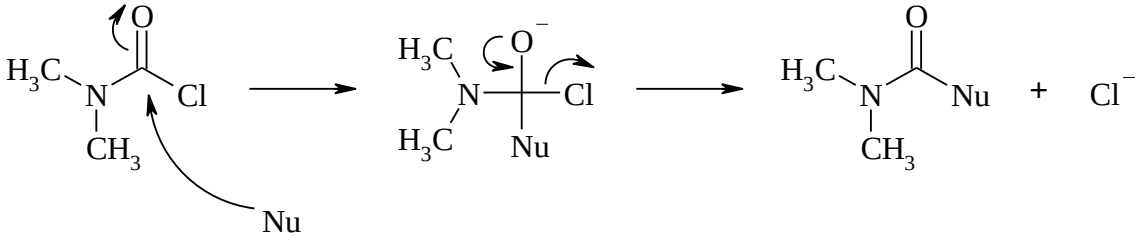
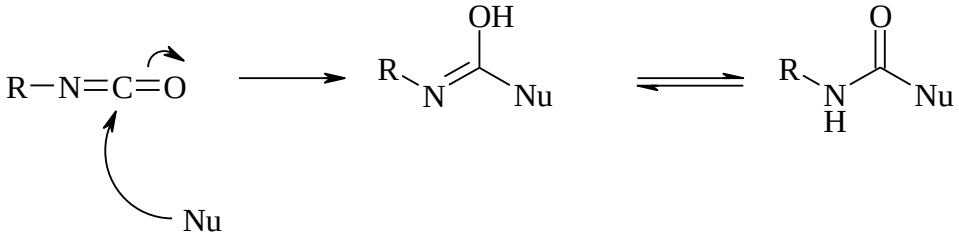
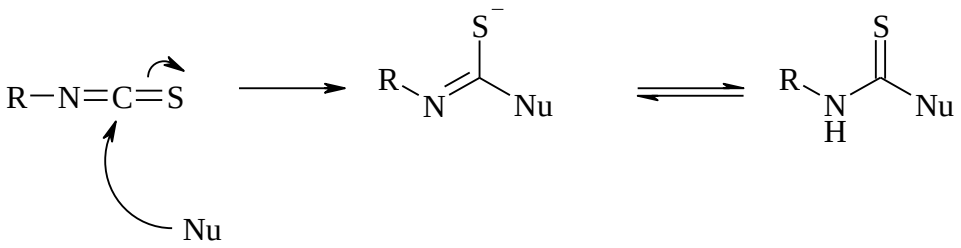
About section of a profiler
Name of the profiler
DNA binding by OECD
Developer; Donator; date; version
Developer: School of Pharmacy and Chemistry, Liverpool John Moores University, UK ***Donator:*** European Chemicals Agency (ECHA); Organization for Economic Co-operation and Development (OECD) ***Version:*** 2.3 December 2016
Relevance/Applicability to endpoint(s)
This profiler is intended to be used for the assessment of endpoints in which covalent binding to DNA has been shown to be the molecular initiating event for low molecular weight chemicals. The profiler has been developed from mechanistic knowledge of the electrophilic chemistry of covalent DNA binding – importantly it has been developed from a systematic review of the literature and not from the analysis of a single toxicological dataset.
Relevance/Applicability to particular chemical classes
This profiler is applicable only to organic chemicals that have a molecular weight less than 1000 g/mol. It is applicable only to the chemical classes for which it contains structural alerts; the absence of a structural alert should not be taken as an absence of toxicity.
Approach used to develop the profiler - Concise but informative description of:
a) The aim of the profiler was to identify structural alerts associated with organic, low molecular weight chemicals capable of forming covalent bonds with DNA. The structural alerts were derived from knowledge of the molecular initiating event - covalently binding to DNA. It was developed from a systematic review of the literature, rather than from the analysis of a single toxicological dataset.
b) The profiler was developed from a mechanistic rationale that the molecular initiating event for covalent bond formation with DNA. Importantly, this was achieved by reviewing the literature relating to the chemistry, rather than an analysis of toxicological datasets.
c) The profiler was developed from an extensive review of the literature relating to the chemistry of covalent bond formation with DNA. A full list of the literature included can be found in the reference listed in section d.
d) An overview of the mechanistic chemistry and underlying principles of the structural alerts within this profiler can be found in: Enoch et al (2010) *A review of the electrophilic reaction chemistry involved in covalent DNA binding.* Critical Reviews in Toxicology, 40, p728-748
Summary description of profiles/alerts within the profiler
It is not possible to provide metrics relating to this profiler as it was not developed from an analysis of toxicological datasets. It was developed from an extensive review of the chemistry related to the formation of a covalent bond between a low molecular weight chemical and DNA.
Similar to other profilers
A number of related endpoint specific profilers exist in the OECD QSAR Toolbox relating to genotoxicity. The ***DNA binding by OECD*** profiler should be used first, with endpoint specific profilers (which have been developed from an analysis of toxicological data) being used to sub-categorise, where possible.

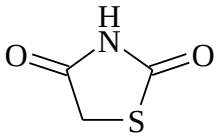
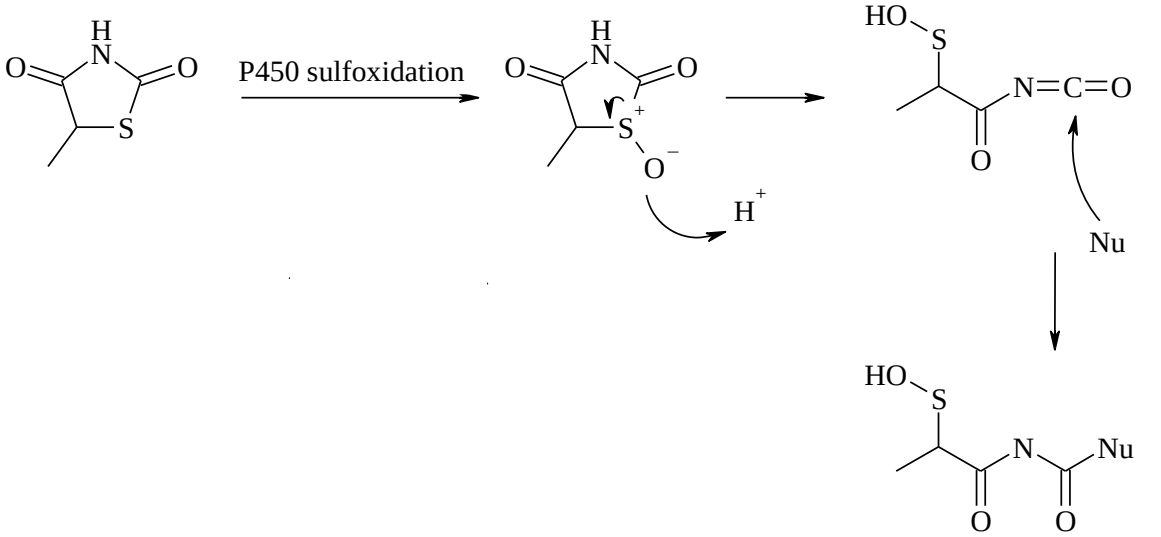
Short description of update version
SMARTS language for describing molecular patterns, i.e. structural boundaries, structural alerts has been implemented in OECD QSAR Toolbox 4.0. As a result ***DNA binding by OECD*** profiler has been rewritten but without modifying the knowledge it is based on. Distinctions are expected in the profiling results between Toolbox v.3.4 and v 4.0 due to different interpretation of the molecular structures, e.g. for heterocyclic/heteroaromatic compounds and the new 2D redactor which allows to define the structure boundaries more correctly according to the description of the categories. An example for category with possible inconsistencies between TB 3.4 and TB 4.0 is the Aromatic azo category. The profiling results in TB 4.0 are expected to be more accurate than these of TB 3.4.
Disclaimer
The structural boundaries used to define the chemical classes (e.g. “Alcohol” – chemical class from “Organic functional group” profiler) or alerting groups responsible for the binding with biological macromolecules (e.g. “Aldehydes” – structural alert for protein binding), represent structural functionalities in the molecule which could be used for building chemical categories for subsequent data gap filling. They are not recommended to be used directly for prediction purposes (as SARs).

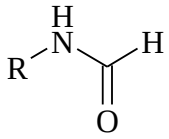
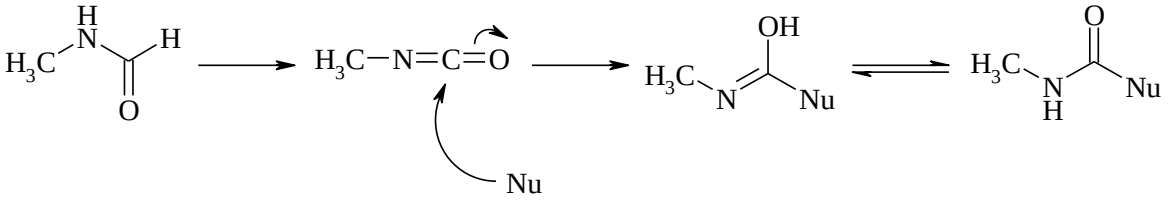
Individual profile/alert	
Name	Acyl halide
Type of profile	Structural alert
Description/applicability domain	 X = halogen R = any carbon, hydrogen
Mechanism	An acylation mechanism has been suggested to be responsible for the ability of acyl halides to bind to DNA macromolecules (Enoch et al 2010).
 Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

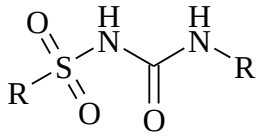
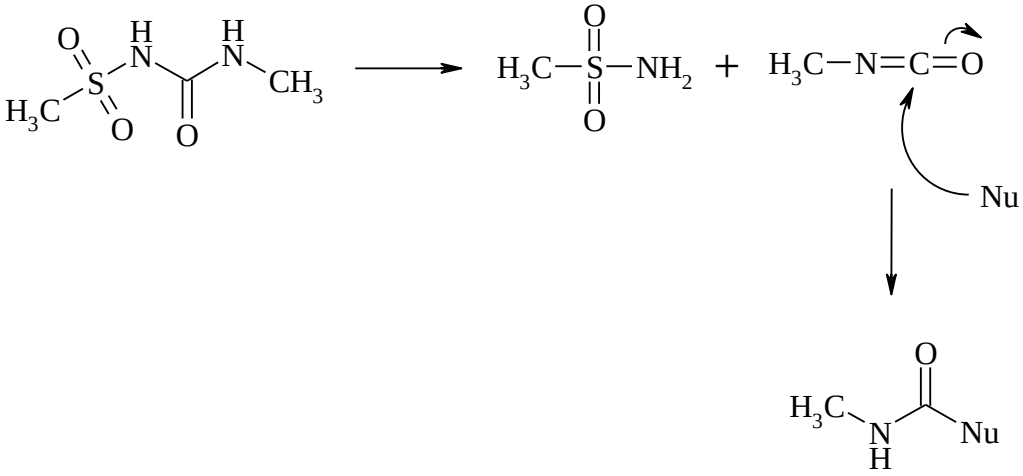
Individual profile/alert	
Name	Alkyl carbamyl halides
Type of profile	Structural alert
Description/applicability domain	 R = any carbon, hydrogen X = F, Cl, Br, I
Mechanism	An acylation mechanism has been suggested as being responsible for the formation of DNA adducts (Enoch et al 2010).
 Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

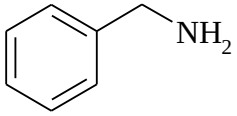
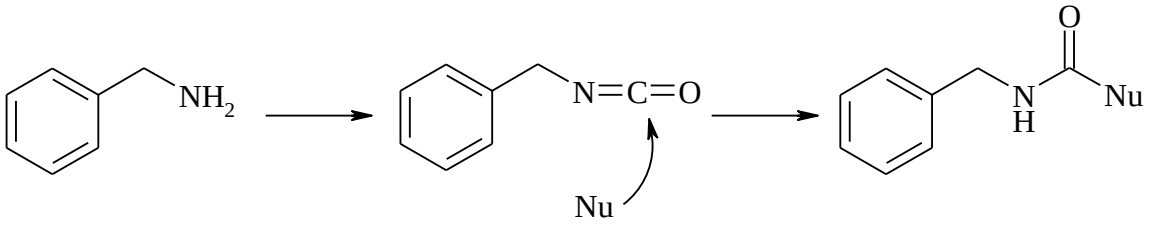
Individual profile/alert	
Name	Isocyanates
Type of profile	Structural alert
Description/applicability domain	R−N=C=O R = any carbon, hydrogen
Mechanism	An acylation mechanism has been suggested as being responsible for the formation of DNA adducts (Enoch et al 2010).
 Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

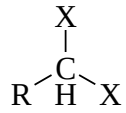
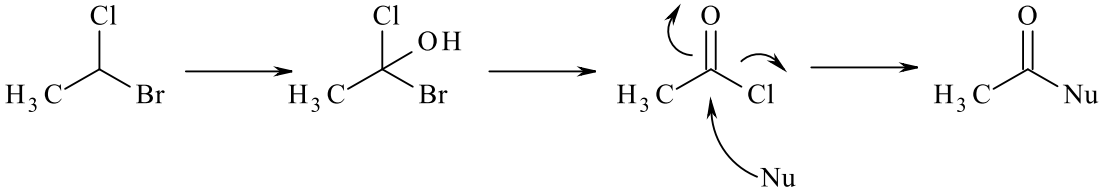
Individual profile/alert	
Name	Isothiocyanates
Type of profile	Structural alert
Description/applicability domain	R—N=C=S R = any carbon, hydrogen
Mechanism	An acylation mechanism has been suggested as being responsible for the formation of DNA adducts (Enoch et al 2010).
 Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

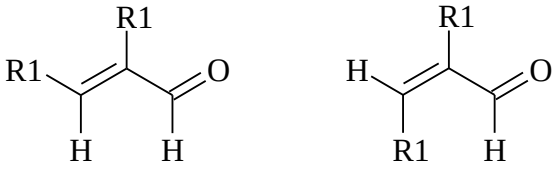
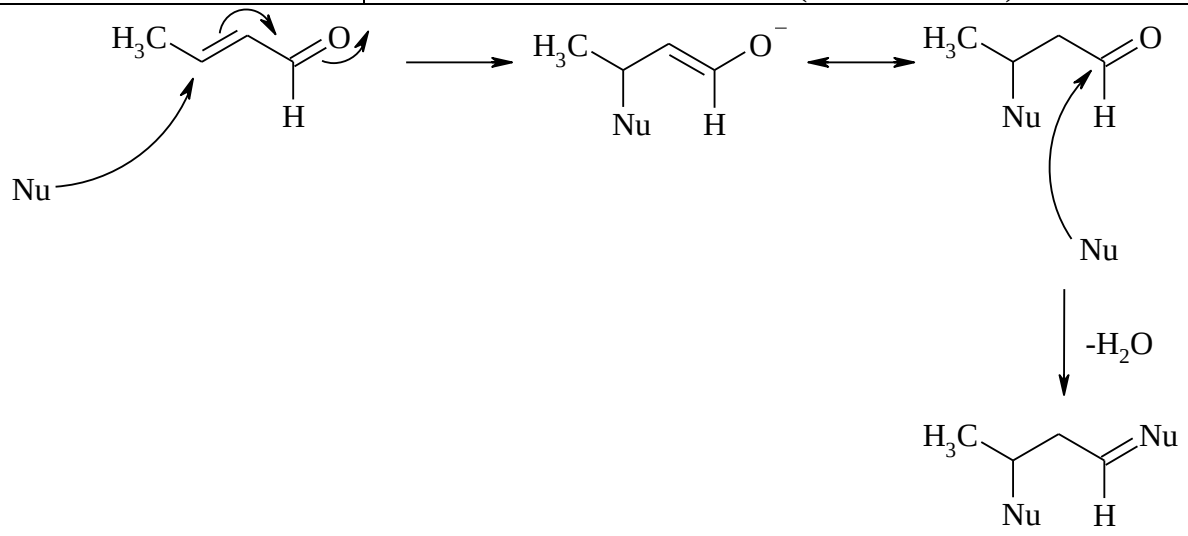
Individual profile/alert	
Name	Thiazolidinediones
Type of profile	Structural alert
Description/applicability domain	
Mechanism	The most likely mechanism for DNA binding that has been suggested involves a P450 mediated sulfoxidation. This reactive intermediate species then undergoes ring scission to produce an isocycanate. This isocyanate undergoes an acylation mechanism with a biological nucleophile such as DNA (Enoch et al 2010).
	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

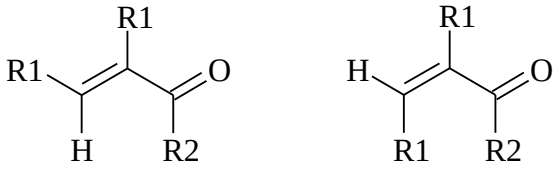
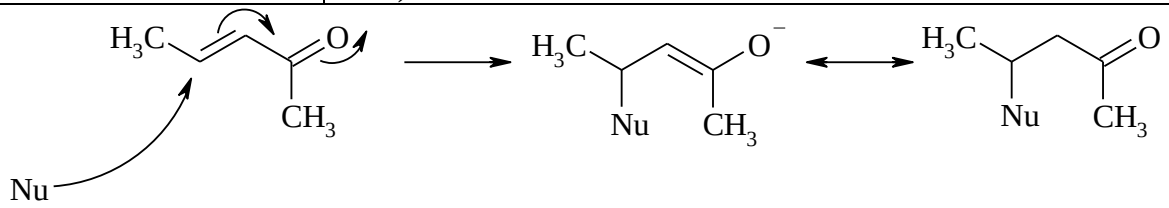
Individual profile/alert	
Name	Formamides
Type of profile	Structural alert
Description/applicability domain	 R = any carbon, hydrogen
Mechanism	Formamides have been suggested to be metabolised by P450 into reactive isocyanate species. Isocyanates have been shown to be able to covalently bind to DNA via an acylation mechanism (Enoch et al 2010).
 Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

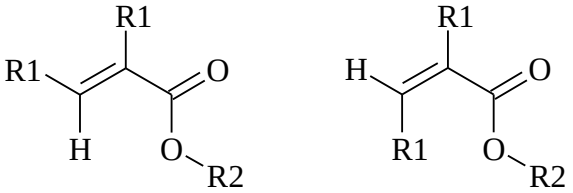
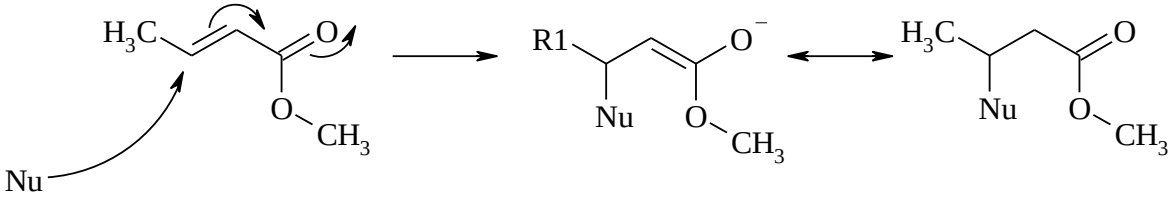
Individual profile/alert	
Name	Sulfonylureas
Type of profile	Structural alert
Description/applicability domain	 R = any carbon, hydrogen
Mechanism	Sulfonylureas have been suggested to be metabolised via amide bond cleavage to produce reactive isocyanate species. Isocycnates have been demonstrated to covalently bind to DNA via a acylation mechanism (Enoch et al 2010).
 Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

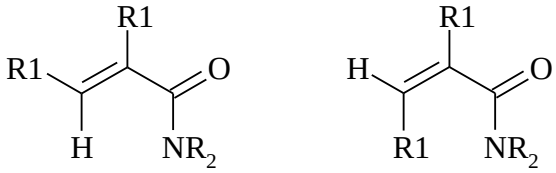
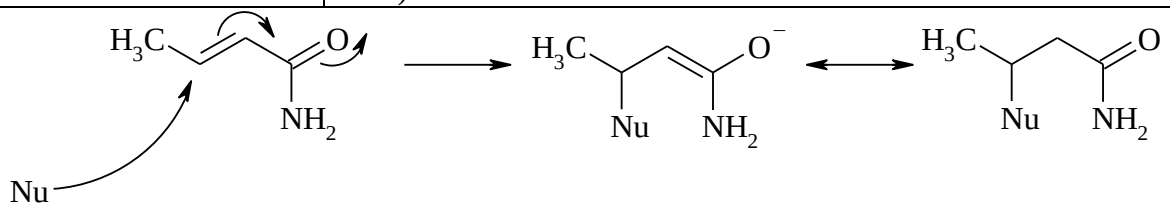
Individual profile/alert	
Name	Benzylamines
Type of profile	Structural alert
Description/applicability domain	
Mechanism	Benzylamines have been shown to be metabolised into several reactive species capable of covalently binding to biological nucleophiles via an acylation mechanism (Enoch et al 2010).
 Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

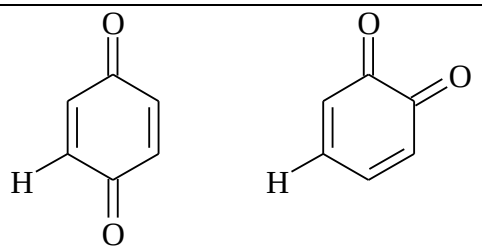
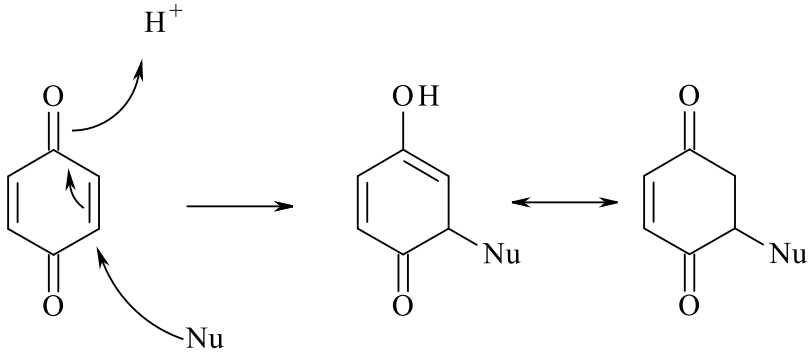
Individual profile/alert	
Name	1,1-Dihaloalkanes
Type of profile	Structural alert
Description/applicability domain	 R = any carbon X = halide
Mechanism	P450 mediated oxidative dehalogenation into an acyl halide has been suggested to be responsible for the toxicity of 1,1-dihaloalkanes. The acyl halide is able to bind DNA via an acylation mechanism (Enoch et al 2010).
 Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

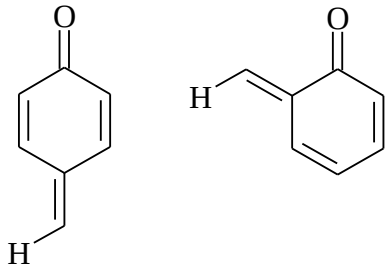
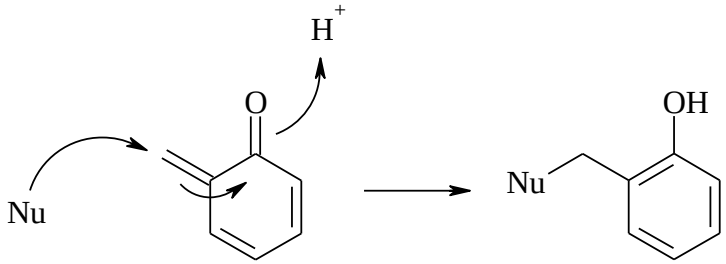
Individual profile/alert	
Name	α,β-Unsaturated aldehydes
Type of profile	Structural alert
Description/applicability domain	 R1 = any carbon atom (except aromatic systems), hydrogen
Mechanism	An initial Michael addition mechanism has been suggested to be primarily responsible for the ability of α,β-unsaturated aldehydes to alkylate DNA. A subsequent Schiff base reaction at the carbonyl can result in cross linked DNA adducts (Enoch et al 2010).
 Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

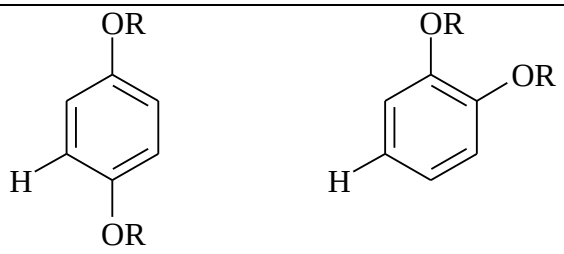
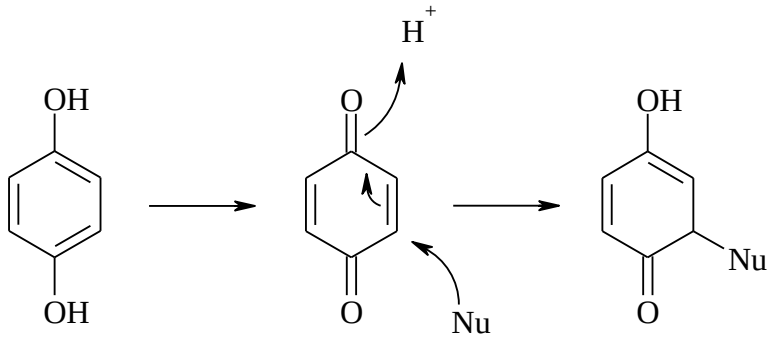
Individual profile/alert	
Name	α,β-Unsaturated ketones
Type of profile	Structural alert
Description/applicability domain	 R1 = any carbon atom (except aromatic systems), hydrogen R2 = any carbon
Mechanism	A Michael addition mechanism has been suggested to be responsible for the ability of α,β-unsaturated ketones to alkylate DNA (Enoch et al 2010).
 Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

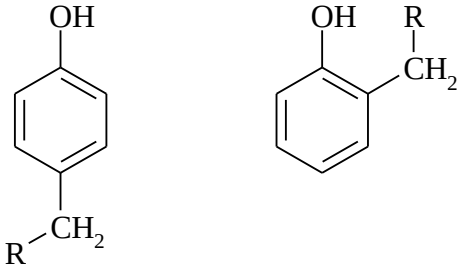
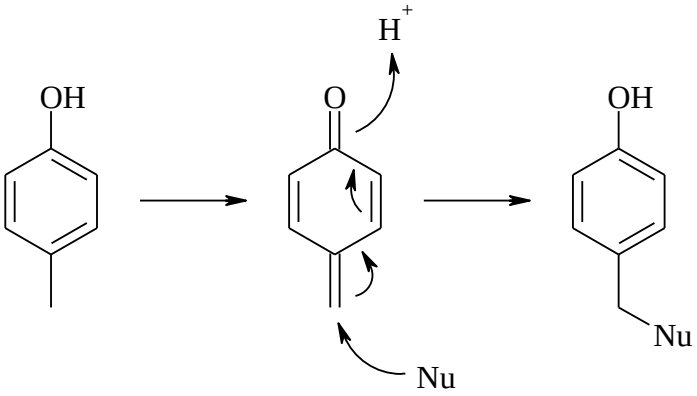
Individual profile/alert	
Name	α,β-Unsaturated esters
Type of profile	Structural alert
Description/applicability domain	 R1 = any carbon atom (except aromatic systems), hydrogen R2 = any carbon
Mechanism	A Michael addition mechanism has been suggested to be responsible for the ability of α,β-unsaturated esters to alkylate DNA (Enoch et al 2010).
 Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

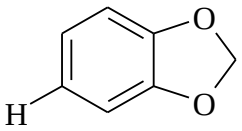
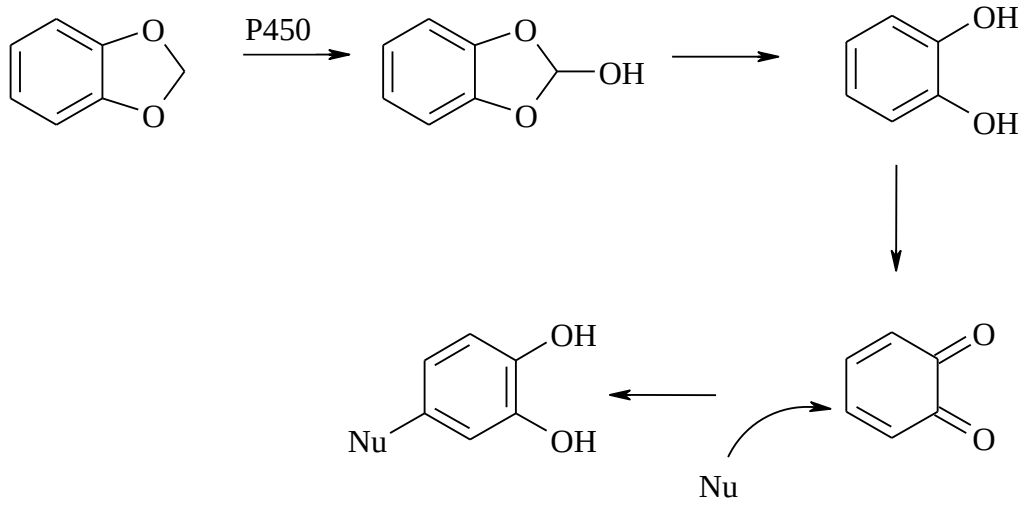
Individual profile/alert	
Name	α,β-Unsaturated amides
Type of profile	Structural alert
Description/applicability domain	 R1 = any carbon atom (except aromatic systems), hydrogen R2 = any carbon, hydrogen
Mechanism	A Michael addition mechanism has been suggested to be responsible for the ability of α,β-unsaturated amides to alkylate DNA (Enoch et al 2010).
 Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

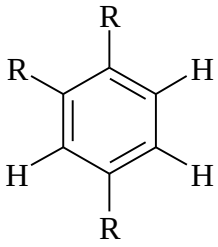
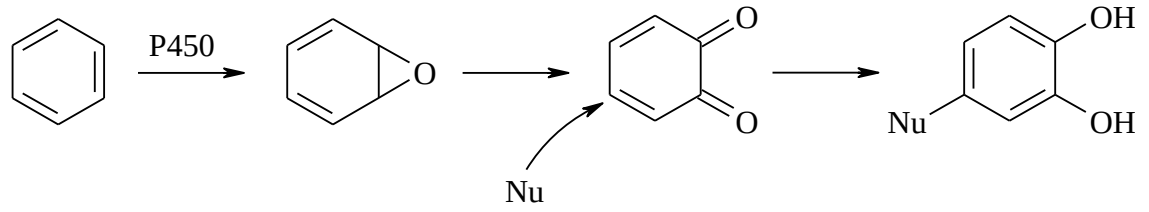
Individual profile/alert	
Name	Quinones
Type of profile	Structural alert
Description/applicability domain	
Mechanism	A Michael addition mechanism has been suggested result in a range of DNA adducts (Enoch et al 2010).
 Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

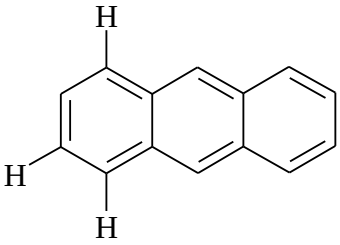
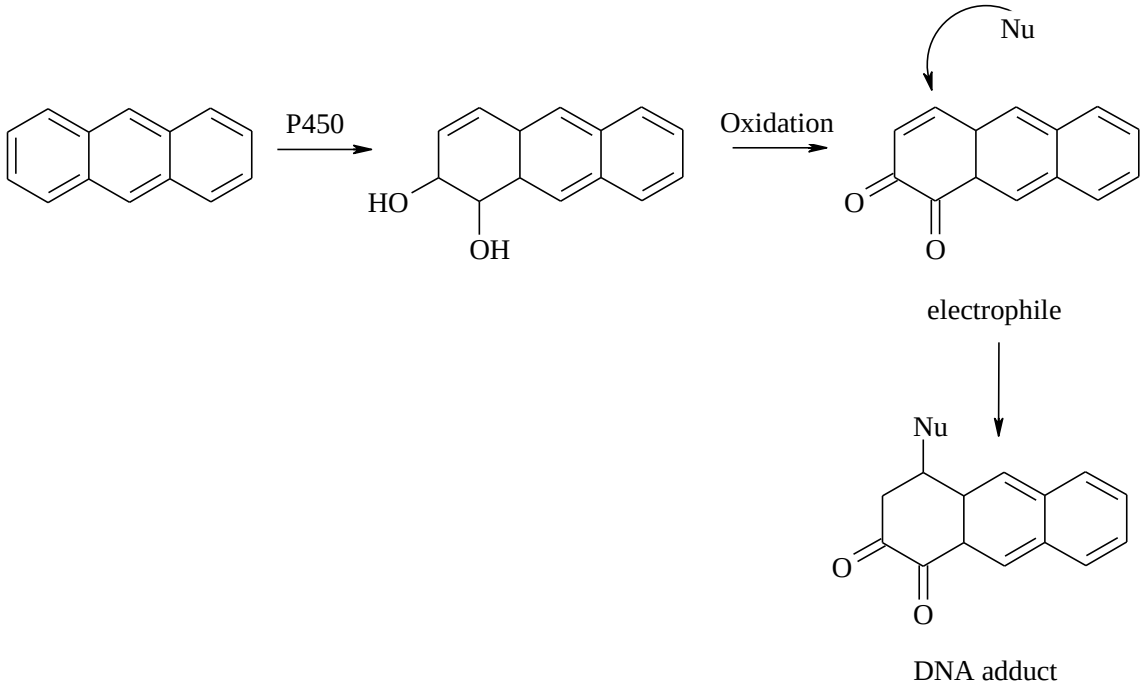
Individual profile/alert	
Name	Quinone-methides
Type of profile	Structural alert
Description/applicability domain	
Mechanism	A Michael addition mechanism has been suggested result in a range of DNA adducts (Enoch et al 2010).
 Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

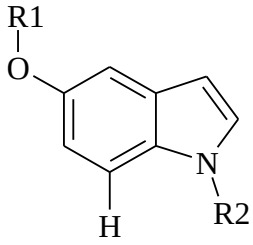
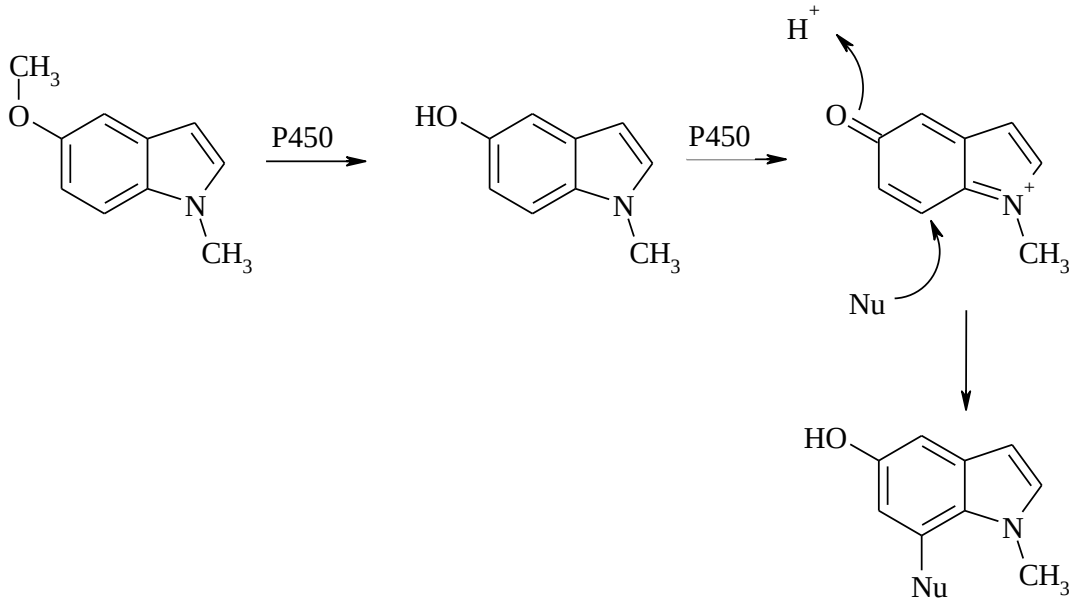
Individual profile/alert	
Name	Hydroquinones
Type of profile	Structural alert
Description/applicability domain	 R = hydrogen, methyl
Mechanism	Hydroquinones have been shown to be oxidised to quinones which can then bind to DNA via a Michael addition mechanism. Methoxy quinones undergo demethylation to produce the corresponding hydroquinone (Enoch et al 2010).
 Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

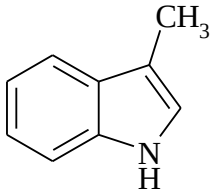
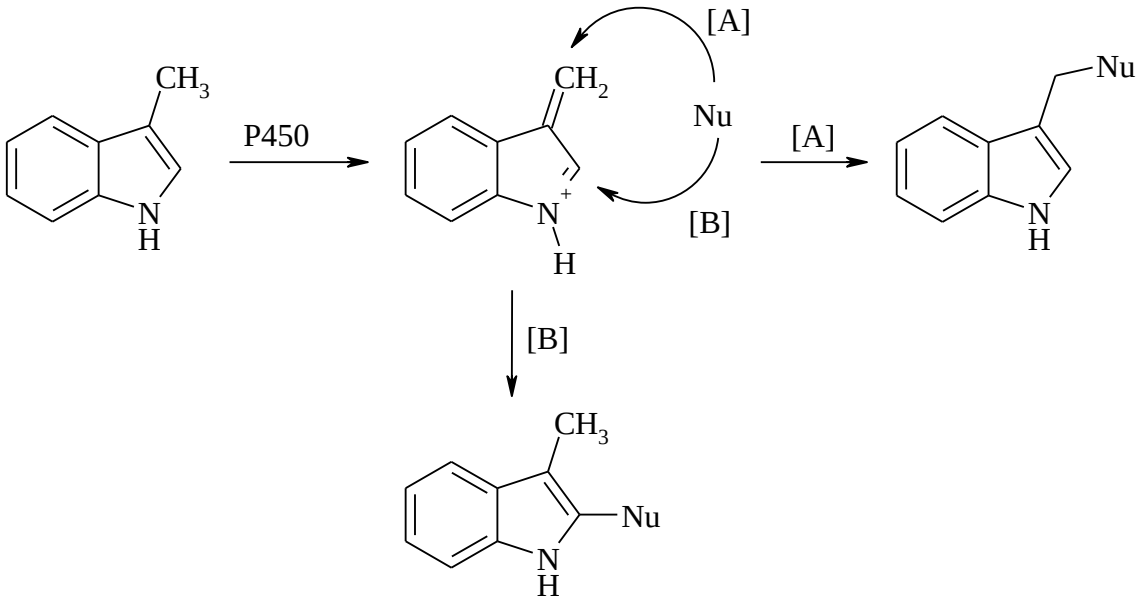
Individual profile/alert	
Name	Hydroquinones
Type of profile	Structural alert
Description/applicability domain	 R = carbon, hydrogen
Mechanism	Oxidation by cytochrome P450 to a quinone methide followed by Michael addition has been suggested to be the primary route of DNA binding (Enoch et al 2010).
 Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

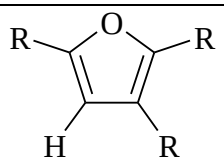
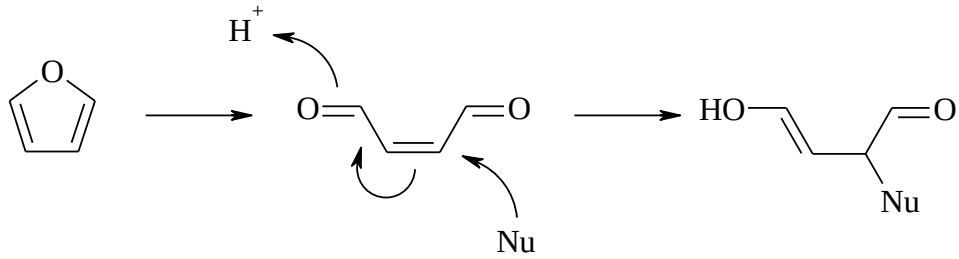
Individual profile/alert	
Name	Methylenedioxyphenyl
Type of profile	Structural alert
Description/applicability domain	
Mechanism	Methylene dioxyphenyl is metabolised by P450 into an ortho substituted phenol. Ortho-substituted phenols can then be further metabolised into quinones which are capable of DNA binding via Michael addition (Enoch et al 2010).
 Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

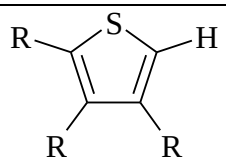
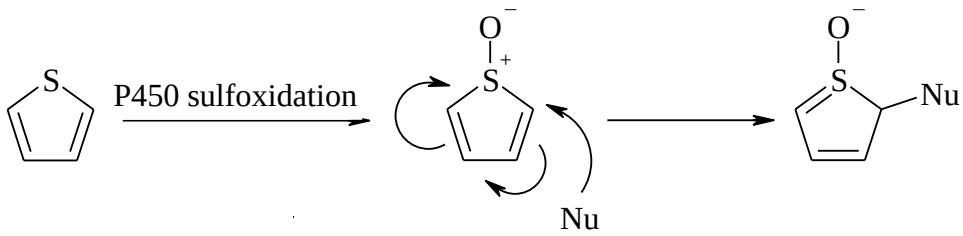
Individual profile/alert	
Name	Arenes
Type of profile	Structural alert
Description/applicability domain	 R = alkyl carbon, hydrogen
Mechanism	A P450 mediated epoxidation followed by conversion to a reactive quinone has been postulated as the primary cause of benzene derivatives ability to bind to biological nucleophiles (via a Michael addition mechanism) (Enoch et al 2010).
 Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

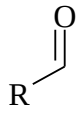
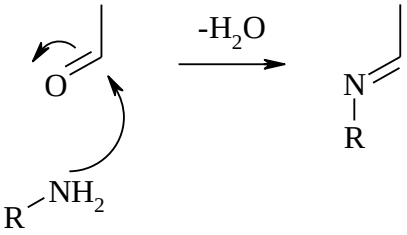
Individual profile/alert	
Name	Polycyclic (PAHs) and heterocyclic (HACs) aromatic hydrocarbons
Type of profile	Structural alert
Description/applicability domain	 (any C in the above structures can be substituted for N)
Mechanism	PAHs and HACs without bay region can undergo oxidation to quinone like species. These quinones are then susceptible to Michael addition reactions (Enoch et al 2010).
 Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

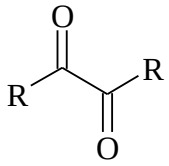
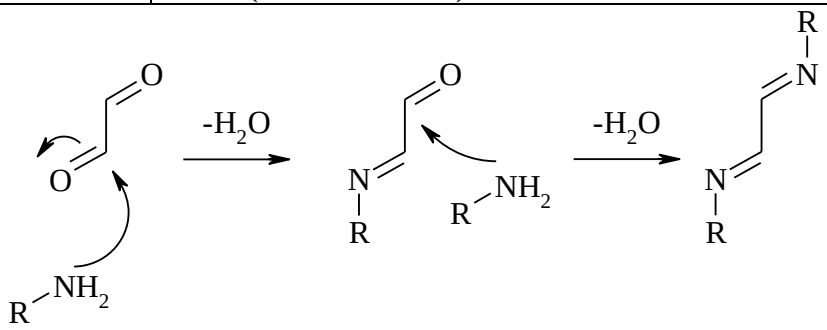
Individual profile/alert	
Name	5-Alkoxyindoles
Type of profile	Structural alert
Description/applicability domain	 R1 = Methyl, Hydrogen R2 = any carbon, hydrogen
Mechanism	A P450 mediated mechanism producing a quinone type species has been suggested as the primary route of toxicity. This species can then react with biological nucleophiles via a Michael addition mechanism (Enoch et al 2010).
	 Nu = biological nucleophile
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

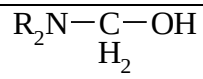
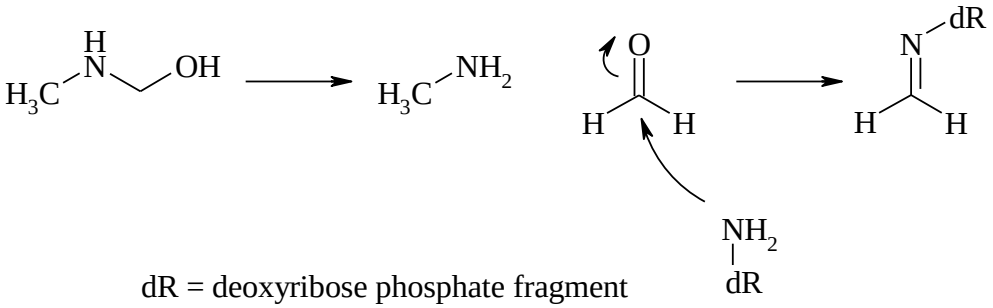
Individual profile/alert	
Name	3-Methylindole derivatives
Type of profile	Structural alert
Description/applicability domain	
Mechanism	P450 dehydrogenation results in an imine-methide intermediate capable of undergoing Michael addition with biological nucleophiles (Enoch et al 2010).
 Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

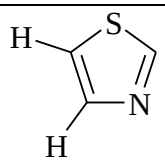
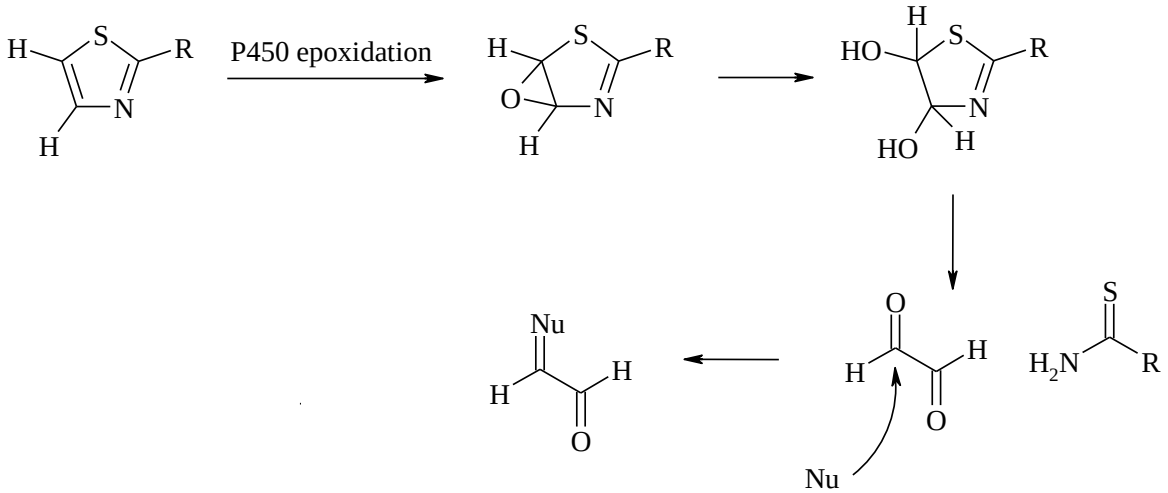
Individual profile/alert	
Name	Furans
Type of profile	Structural alert
Description/applicability domain	 R = hydrogen, any carbon expect the following R ≠ -NHR1 (R1 = any carbon, oxygen, hydrogen), -N(R1)$_2$ (R1 = any combination of methyl or ethyl), -NO$_2$, -NO, -N=NR1 (R1 = any carbon, hydrogen)
Mechanism	A cytochrome P450 mediated ring opening reaction producing a reactive dial capable of undergoing Michael addition has been proposed (Enoch et al 2010).
 Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

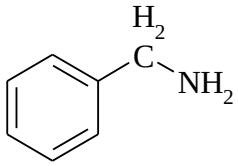
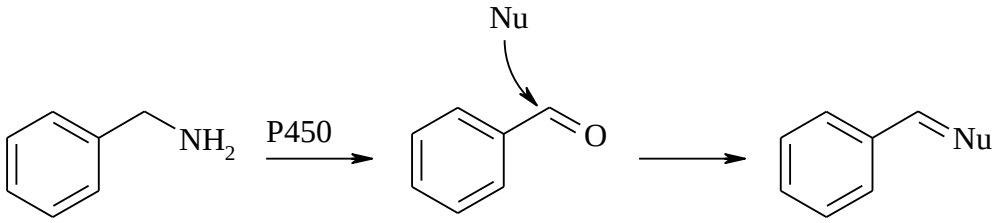
Individual profile/alert	
Name	Thiophenes
Type of profile	Structural alert
Description/applicability domain	 R = hydrogen, any carbon expect the following R ≠ -NHR1 (R1 = any carbon, oxygen, hydrogen), -N(R1)$_2$ (R1 = any combination of methyl or ethyl), -NO$_2$, -NO, -N=NR1 (R1 = any carbon, hydrogen)
Mechanism	A P450 mediated sulfoxidation followed by Michael type addition has been suggested as a potential mechanism leading to DNA alkylation (Enoch et al 2010).
 Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

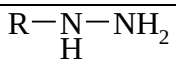
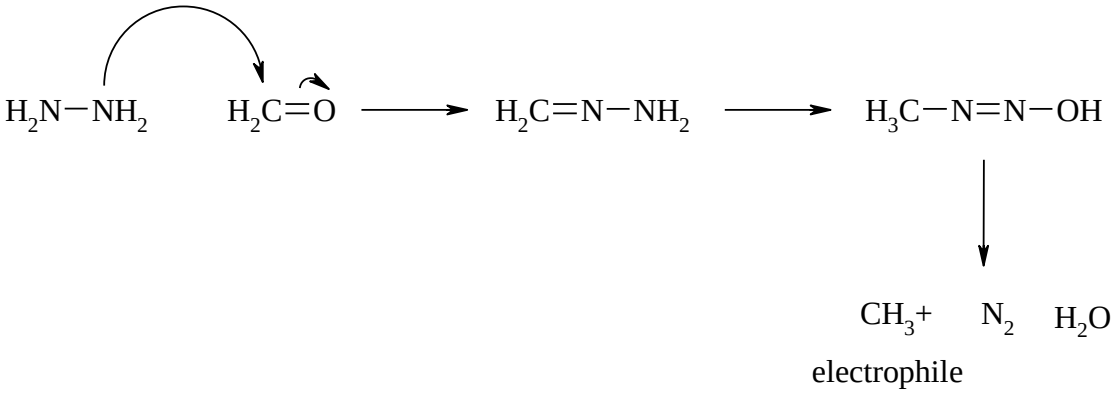
Individual profile/alert	
Name	Mono-aldehydes
Type of profile	Structural alert
Description/applicability domain	 R = any carbon, hydrogen
Mechanism	Mono aldehydes undergo Schiff base formation (Enoch et al 2010).
	 R = DNA chain
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

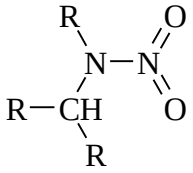
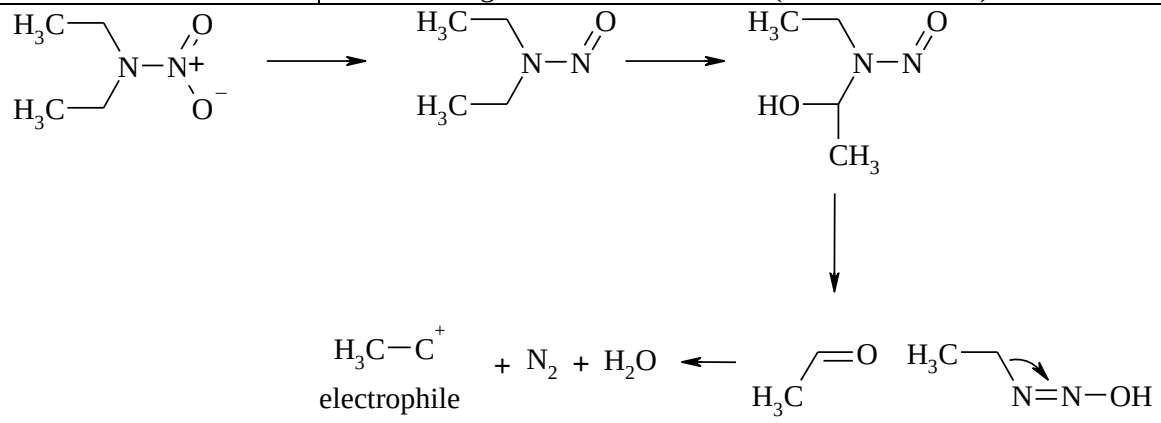
Individual profile/alert	
Name	α-β-Dicarbonyl
Type of profile	Structural alert
Description/applicability domain	 R = any carbon, hydrogen
Mechanism	A multi-step Schiff base mechanism leads to cross-linking of DNA chains (Enoch et al 2010).
 R = DNA chain	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

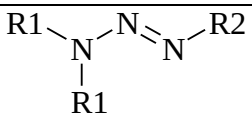
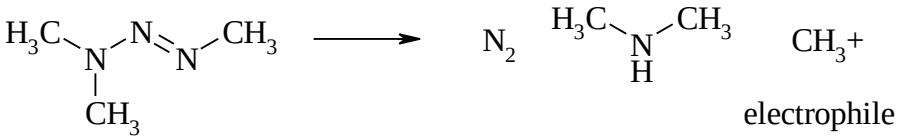
Individual profile/alert	
Name	*N*-methylol derivatives
Type of profile	Structural alert
Description/applicability domain	 R = hydrogen, alkyl C, aryl C
Mechanism	*N*-methylol derivatives have been suggested to be genotoxic via hydrolysis into formaldehyde. Formaldehyde then undergoes DNA binding via a Schiff base reaction (Enoch et al 2010).
 dR = deoxyribose phosphate fragment	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

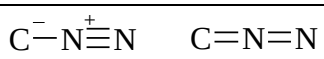
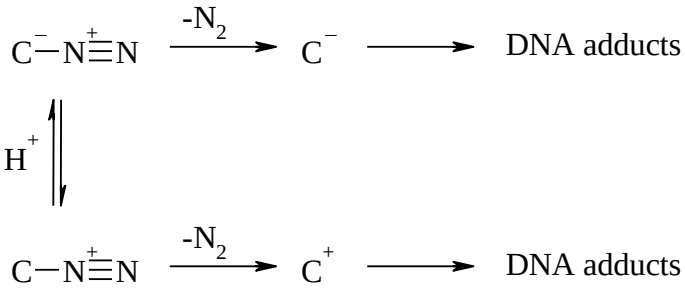
Individual profile/alert	
Name	Thiazoles
Type of profile	Structural alert
Description/applicability domain	
Mechanism	Epoxidation followed by ring scission have been suggested to produce potentially toxic α,β-unsaturated carbonyl metabolites which can bind DNA via a Schiff base mechanism (Enoch et al 2010).
	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

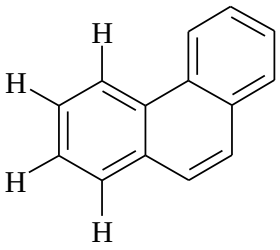
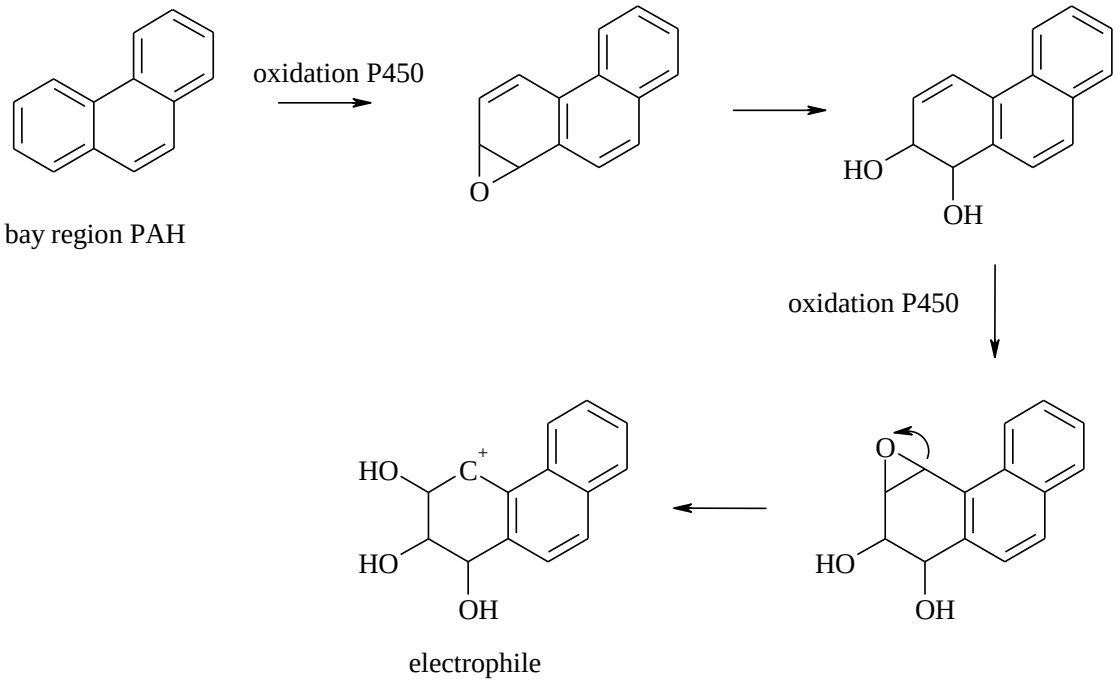
Individual profile/alert	
Name	Benzylamines
Type of profile	Structural alert
Description/applicability domain	
Mechanism	Benzylamines have been shown to be metabolised into several reactive species capable of covalently binding to biological nucleophiles via a Schiff base mechanism (Enoch et al 2010).
	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

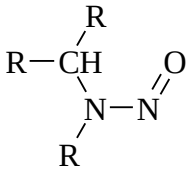
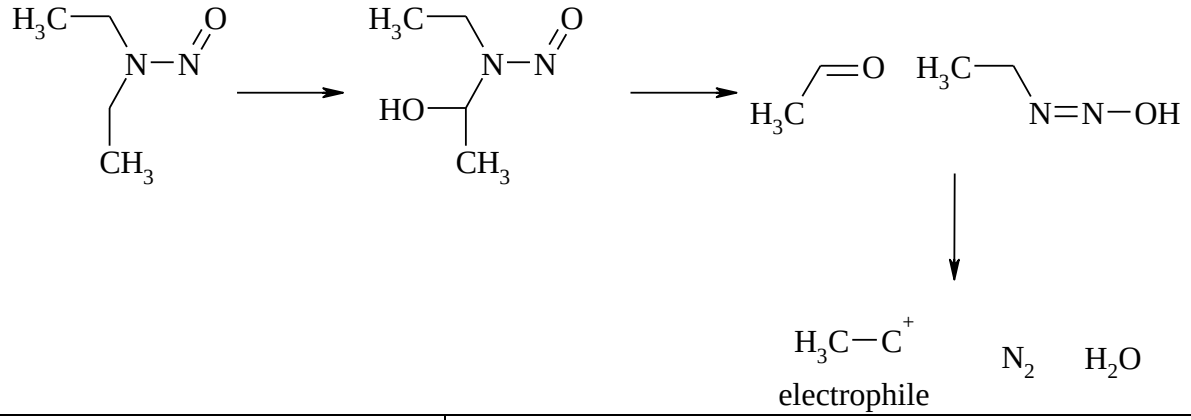
Individual profile/alert	
Name	Hydrazine
Type of profile	Structural alert
Description/applicability domain	 R = any atom
Mechanism	Formaldehyde hydrozone formation via a Schiff base mechanism followed by DNA alkylation via an S_N1 mechanism has been suggested to lead to DNA alkylation (Enoch et al 2010).
 electrophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

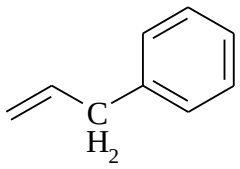
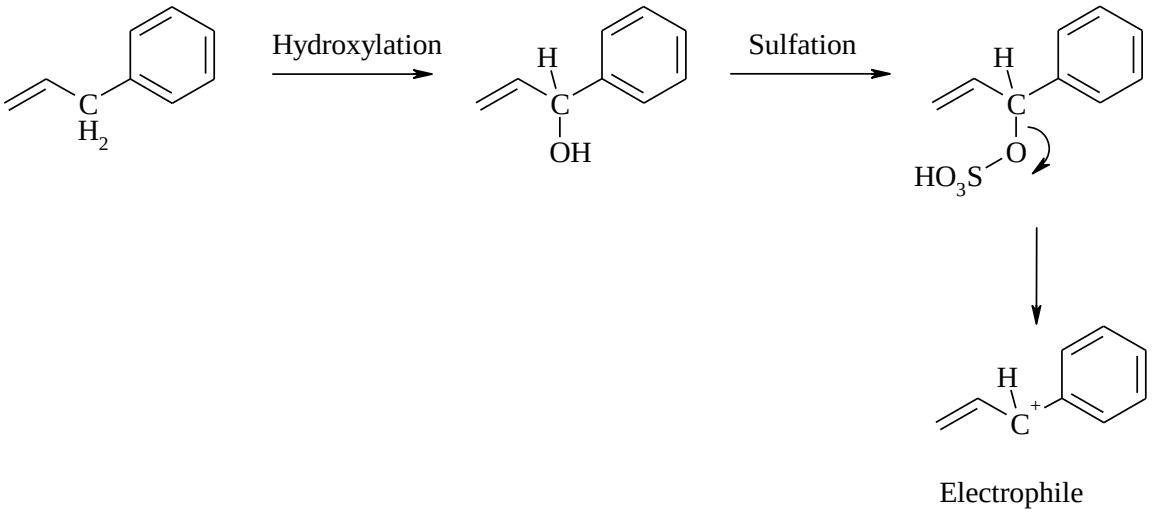
Individual profile/alert	
Name	Aliphatic *N*-Nitro
Type of profile	Structural alert
Description/applicability domain	 R = any carbon or hydrogen
Mechanism	DNA have been suggested to be formed via the reduction of the nitro group to a nitroso and then formation of a carbenium ion resulting in DNA binding via an S_N1 mechanism (Enoch et al 2010).
 electrophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

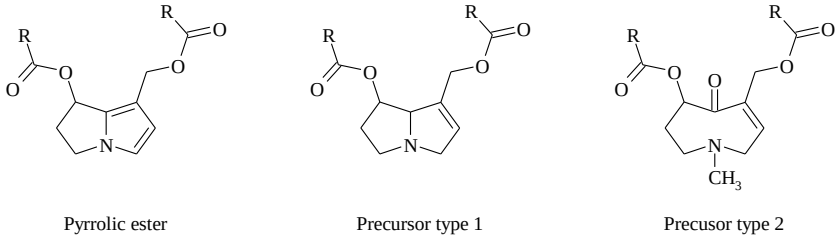
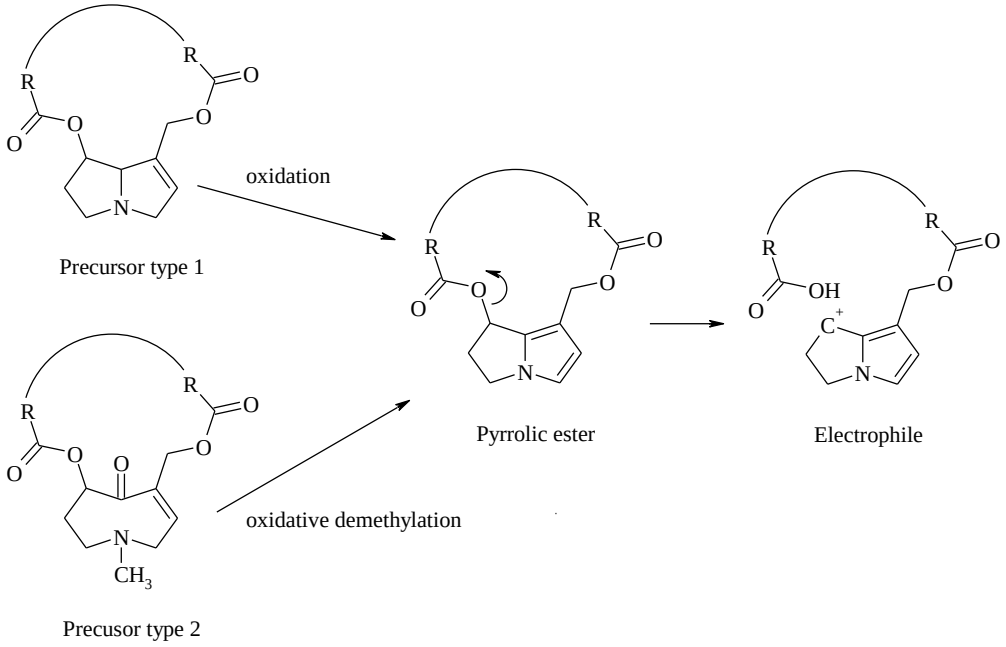
Individual profile/alert	
Name	Triazenes
Type of profile	Structural alert
Description/applicability domain	 R1 = any carbon, hydrogen R2 = alkyl
Mechanism	Triazenes in which R2 is an alkyl group have been suggested to alkylate DNA via an S_N1 mechanism (after the production of a carbocation) (Enoch et al 2010).
 electrophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

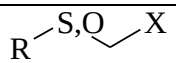
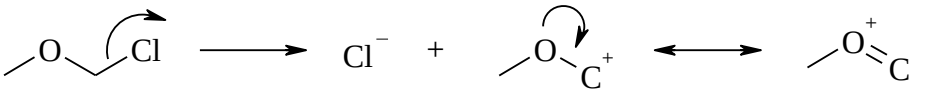
Individual profile/alert	
Name	Diazoalkanes
Type of profile	Structural alert
Description/applicability domain	 (either isomer is acceptable)
Mechanism	Two possible mechanisms have been suggested that can lead to DNA adducts and cleavage. Both mechanisms produce a reactive carbon ion as shown (and can be considered S_N1 type mechanisms) (Enoch et al 2010).
	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

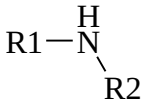
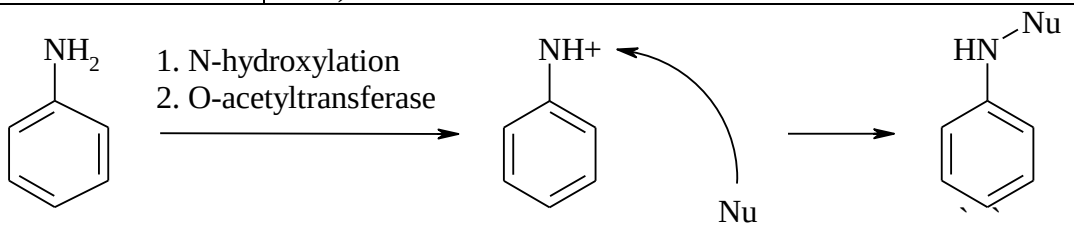
Individual profile/alert	
Name	Polycyclic (PAHs) and heterocyclic (HACs) aromatic hydrocarbons
Type of profile	Structural alert
Description/applicability domain	 (any C in the above structures can be substituted for N)
Mechanism	Bay region PAHs and HACs undergo P450 mediated oxidation to produce a reactive carbenium ion. Alkylation then occurs via an S_N1 mechanism (Enoch et al 2010).
 bay region PAH oxidation P450 oxidation P450 electrophile Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

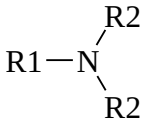
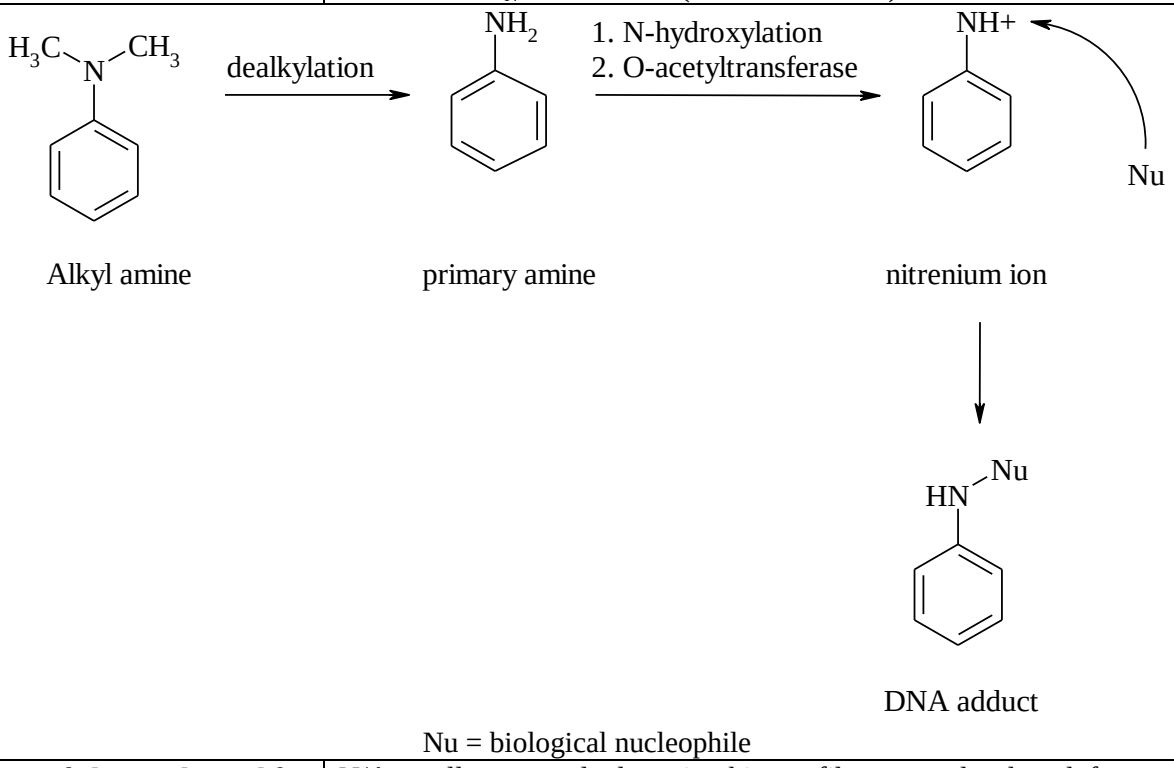
Individual profile/alert	
Name	Nitroso
Type of profile	Structural alert
Description/applicability domain	 R = any carbon or hydrogen
Mechanism	An S_N1 mechanism has been suggested as a route to DNA binding. The alkyl R group can undergo α-hydroxylation metabolism producing a carbenium ion leading to an S_N1 alkylation reaction (Enoch et al 2010).
 electrophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

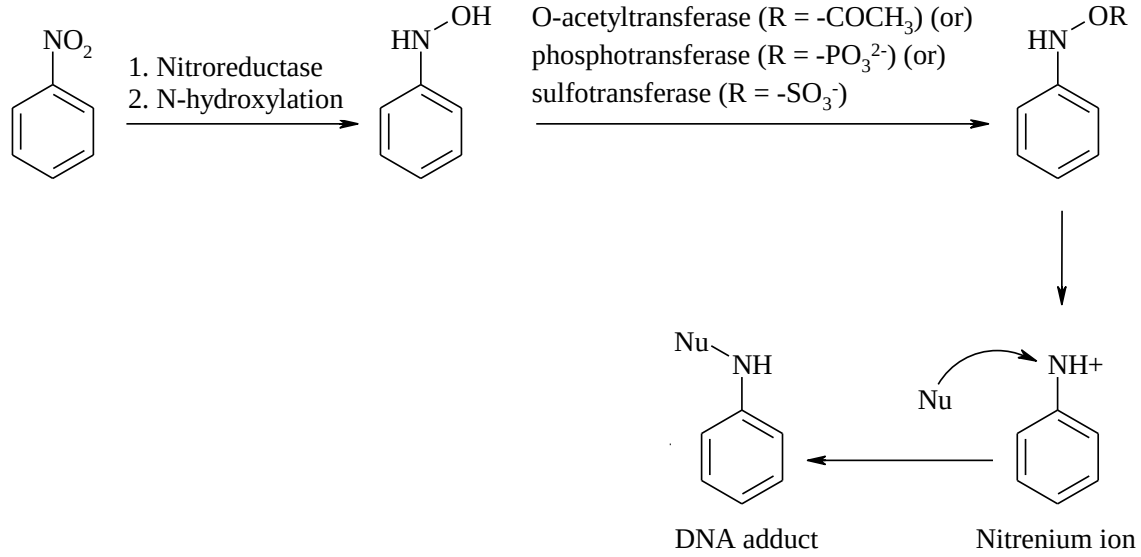
Individual profile/alert	
Name	Allyl benzenes
Type of profile	Structural alert
Description/applicability domain	
Mechanism	Allyl benzenes have been suggested to be metabolised in reactive carbenium ions via initial hydroxylation followed by sulfation. The carbenium ion can then alkylate DNA via an S_N1 mechanism (Enoch et al 2010).
	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

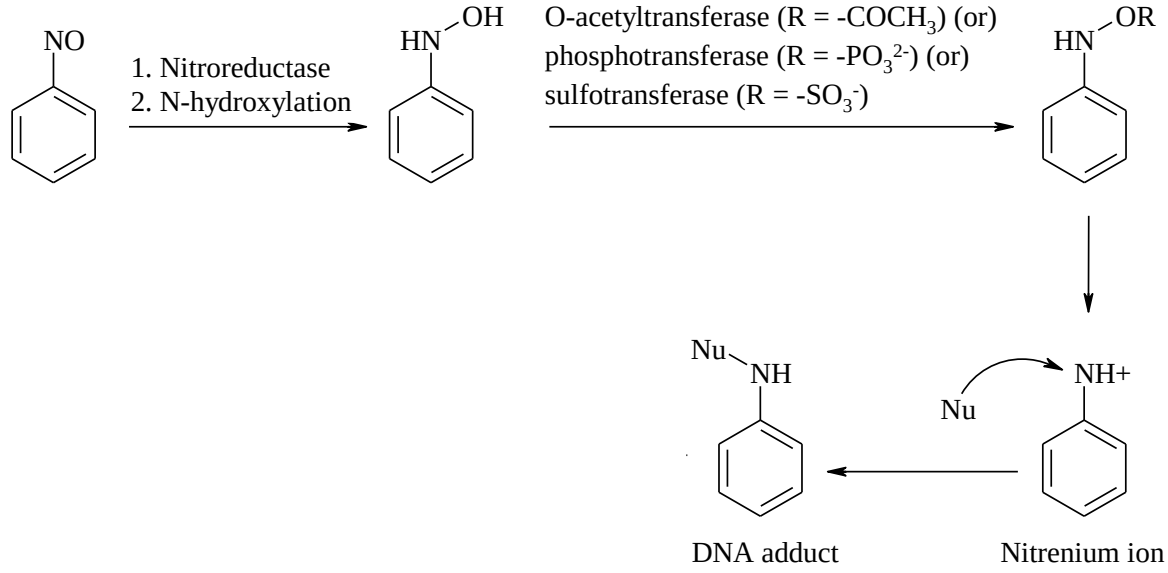
Individual profile/alert	
Name	Pyrrolizidine alkaloids
Type of profile	Structural alert
Description/applicability domain	 Pyrrolic ester Precursor type 1 Precusor type 2 R = alkyl (the two R groups can be linked to form a cyclic system)
Mechanism	Pyrrolizidine alkaloids have been suggested to be capable of binding to DNA via metabolic oxidation into pyrrolic esters derivatives. The pyrrolic ester derivative has been shown to rearrange producing a carbenium ion capable of undergoing an S_N1 reaction (Enoch et al 2010).
 Precursor type 1 oxidation Pyrrolic ester Electrophile oxidative demethylation Precusor type 2	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

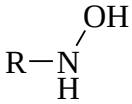
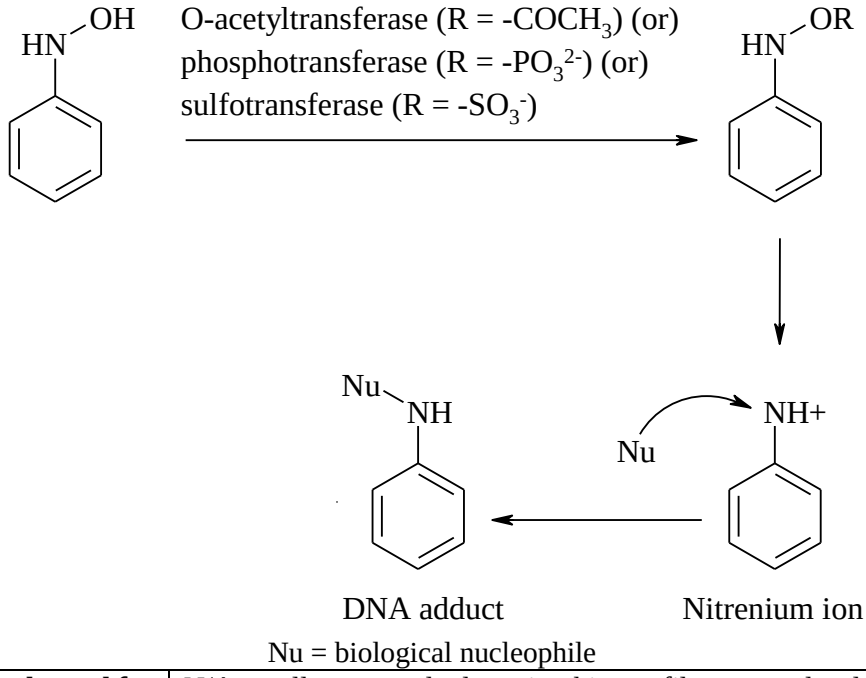
Individual profile/alert	
Name	α-Halo ethers (including α-halo thioethers)
Type of profile	Structural alert
Description/applicability domain	 R = any carbon X = F, Cl, Br, I
Mechanism	A direct acting S_N1 mechanism has been suggested as being responsible for the formation of DNA adducts. This mechanism involves the formation of a resonance stabilised oxonium (sulfonium) / carbenium ion (Enoch et al 2010).
 carbenium ion oxonium ion resonance stabilised electrophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

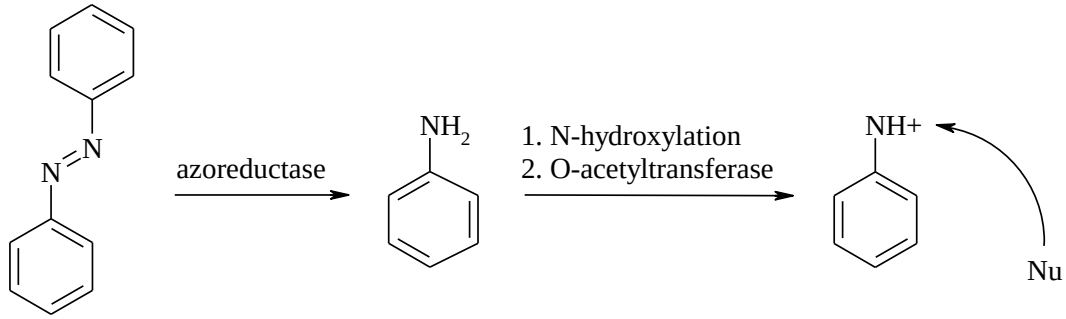
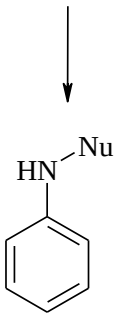
Individual profile/alert	
Name	Aromatic amines (primary or secondary)
Type of profile	Structural alert
Description/applicability domain	 R1 = any aromatic or hetero-aromatic (connected via a carbon atom) R2 = hydrogen, alkyl carbon
Mechanism	Primary aromatic amines undergo metabolism to a reactive nitrenium ion. This ion can bind to DNA via an S_N1 mechanism (Enoch et al 2010).
 primary amine nitrenium ion DNA adduct Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

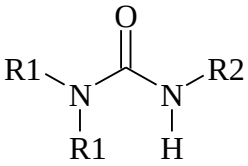
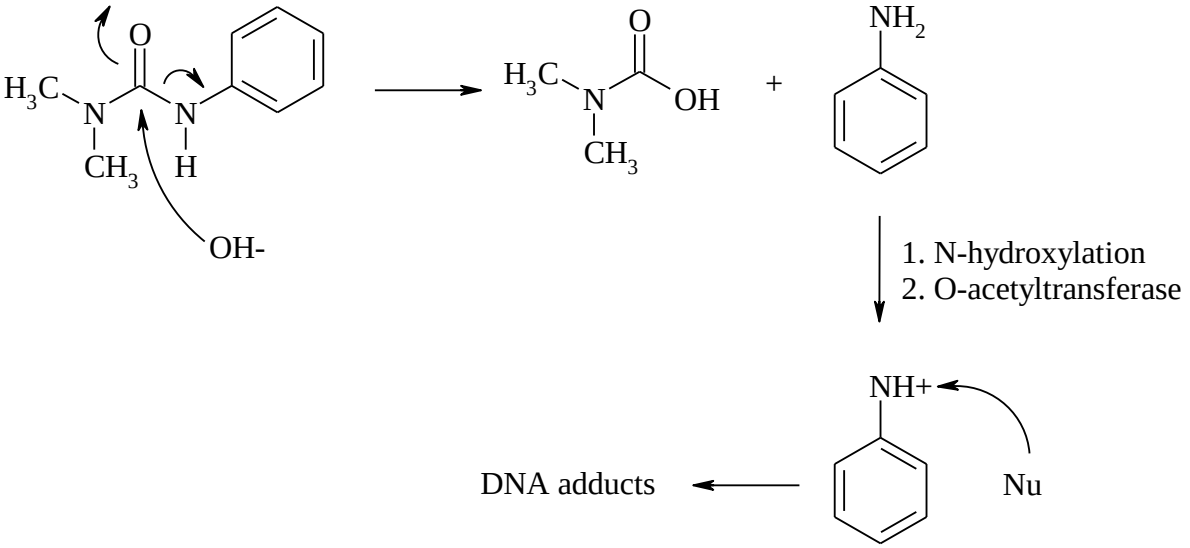
Individual profile/alert	
Name	Protected aromatic amines
Type of profile	Structural alert
Description/applicability domain	 R1 = any aromatic or hetero-aromatic (connected via a carbon atom) R2 = any combination of methyl, ethyl
Mechanism	Protected secondary and tertiary aromatic amines (methyl and ethyl) undergo metabolism to a reactive nitrenium ion. This ion can bind to DNA via an S_N1 mechanism (Enoch et al 2010).
 Alkyl amine primary amine nitrenium ion DNA adduct Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

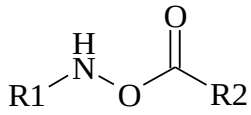
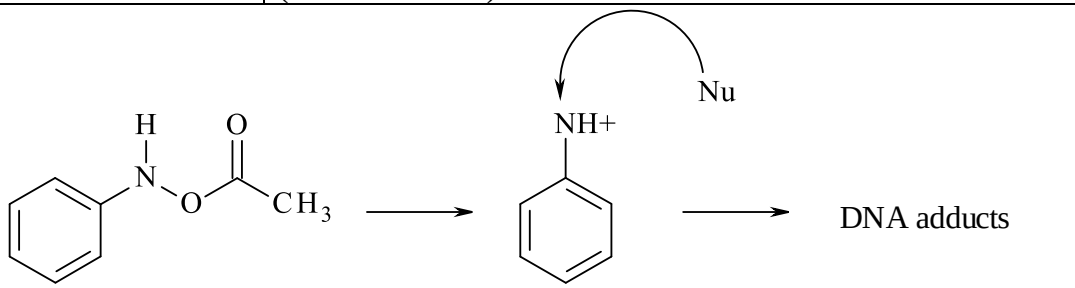
Individual profile/alert	
Name	Aromatic nitros
Type of profile	Structural alert
Description/applicability domain	$R-NO_2$ R = any aromatic or hetero-aromatic (connected via a carbon atom)
Mechanism	Aromatic nitro groups are metabolised into an *N*-hydroxylated intermediate which subsequently undergoes either acetyl-, phospo- or sulfotransferase. This species then produces the electrophilic nitrenium ion which is capable of reacting with DNA via an S_N1 mechanism (Enoch et al 2010).
 Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

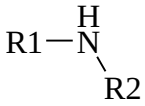
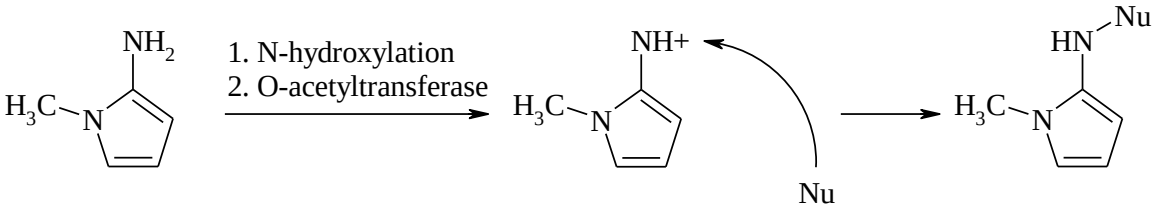
Individual profile/alert	
Name	Aromatic nitrosos
Type of profile	Structural alert
Description/applicability domain	R—NO R = any aromatic or hetero-aromatic (connected via a carbon atom)
Mechanism	Aromatic nitroso compounds are reduced and then hydroxylated to an *N*-hydroxylamine intermediate. This species is then further metabolised by one of three potential transferases, which themselves produce the reactive nitrenium ion which can bind DNA via an S_N1 mechanism (Enoch et al 2010).
 Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

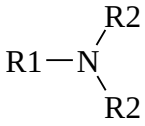
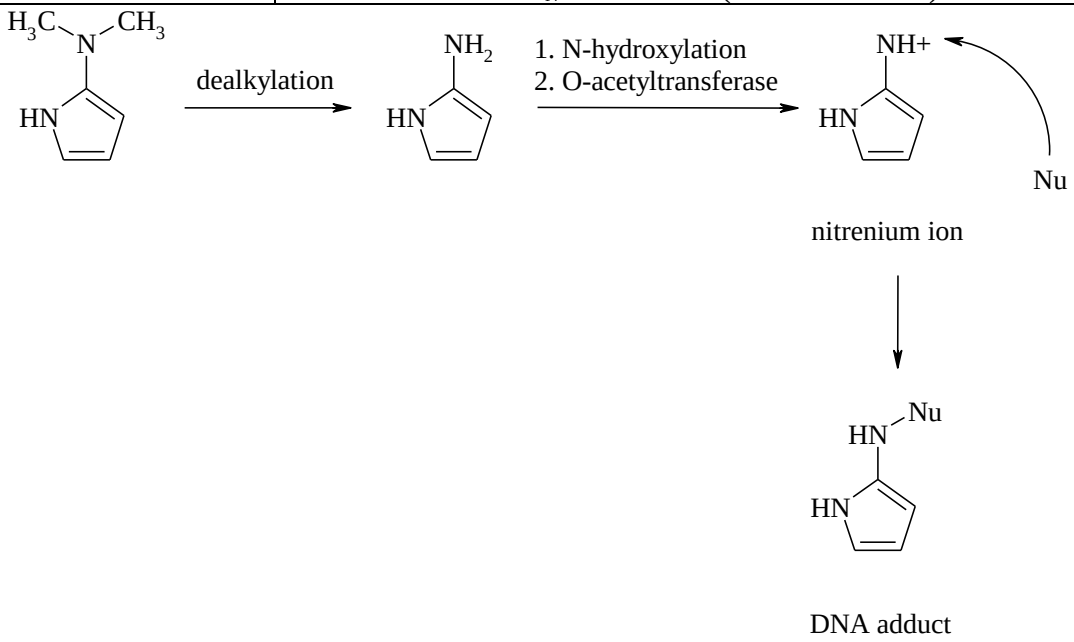
Individual profile/alert	
Name	Aromatic *N*-hydroxylamines
Type of profile	Structural alert
Description/applicability domain	 R = any aromatic or hetero-aromatic (connected via a carbon atom)
Mechanism	Aromatic *N*-hydroxylated groups are metabolised by either acetyl-, phospo- or sulfotransferase. These species then produce the electrophilic nitrenium ion which is capable of reacting with DNA via an S_N1 mechanism (Enoch et al 2010).
 Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

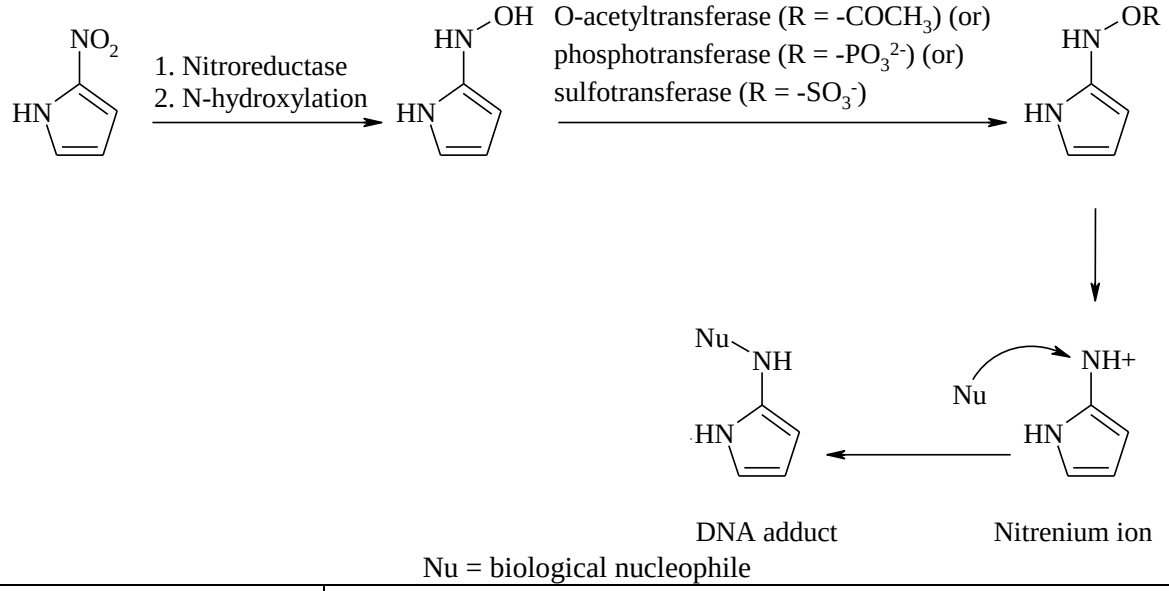
Individual profile/alert	
Name	Aromatic azos
Type of profile	Structural alert
Description/applicability domain	R1—N=N—R2 R1 = any aromatic or hetero-aromatic (connected via a carbon atom) R2 = any carbon atom, hydrogen
Mechanism	The most likely mechanism is phase one metabolism of the azo via azoreductase producing an aromatic amine which then undergoes metabolism into the DNA reactive (via an S_N1 mechanism) nitrenium ion (Enoch et al 2010).
 aromatic azo primary amine nitrenium ion  DNA adduct Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

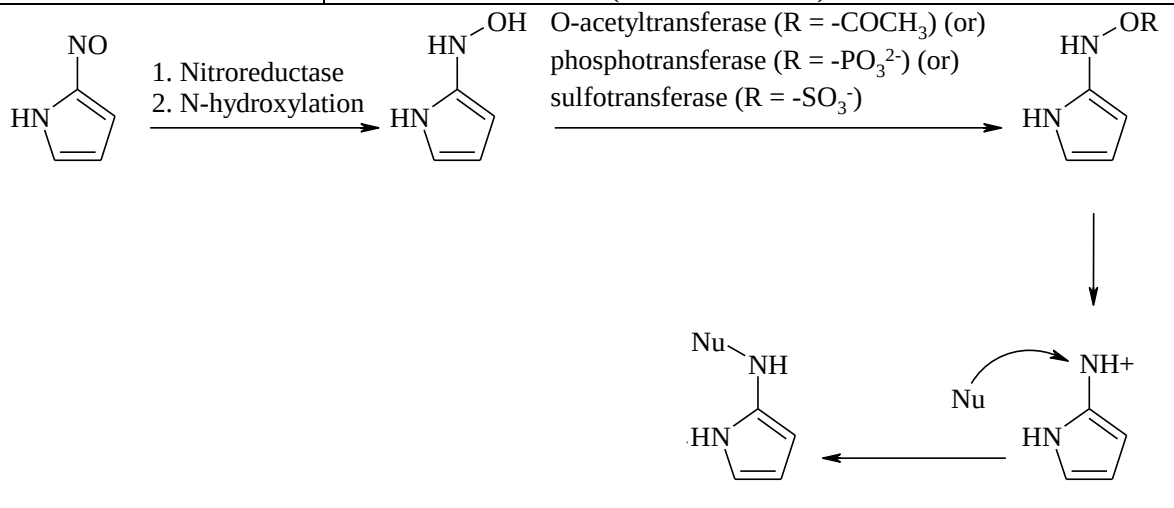
Individual profile/alert	
Name	Aromatic phenylureas
Type of profile	Structural alert
Description/applicability domain	 R1 = carbon or hydrogen R2 = any aromatic or hetero-aromatic (connected via a carbon atom)
Mechanism	Hydrolysis of the amide bond to produce an aromatic amine moiety has been suggested to be responsible for the toxicity of chemicals containing this alert. The formation of the nitrenium ion results in DNA binding via an S_N1 mechanism (Enoch et al 2010).
 Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

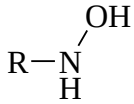
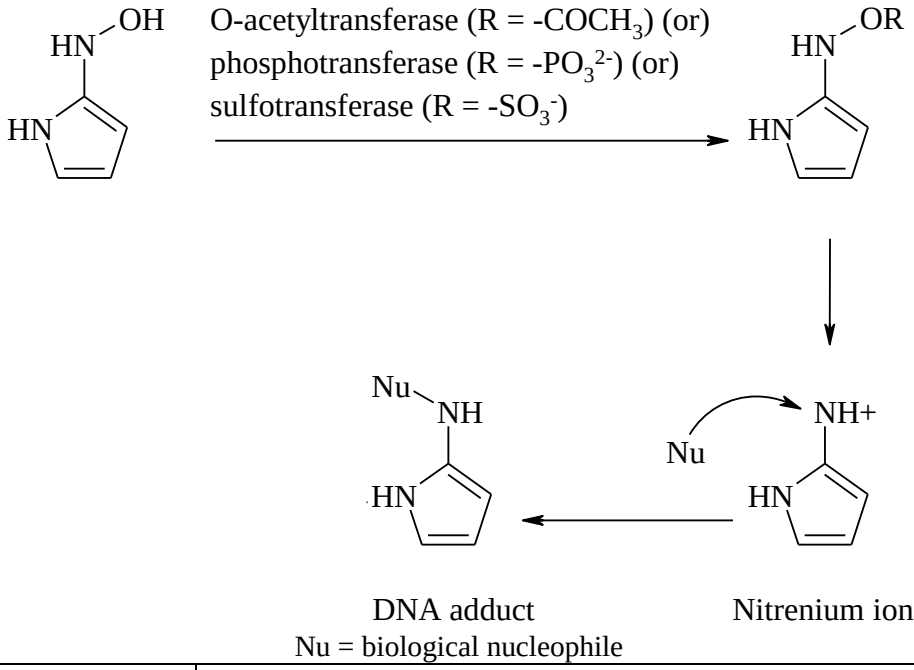
Individual profile/alert	
Name	Ester aromatic hydroxylamines
Type of profile	Structural alert
Description/applicability domain	 R1 = any aromatic or hetero-aromatic (connected via a carbon atom) R2 = any carbon atom
Mechanism	Desterification to produce a reactive nitrenium ion capable of reacting with DNA via an S_N1 mechanism is the most likely mechanism (Enoch et al 2010).
 biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

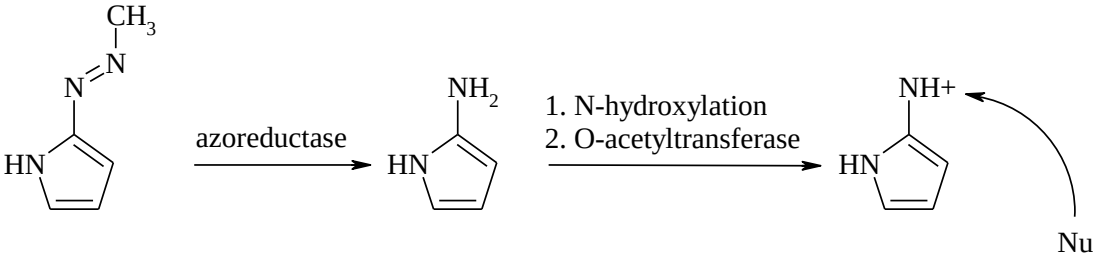
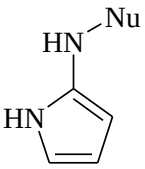
Individual profile/alert	
Name	Heterocyclic amines (primary or secondary)
Type of profile	Structural alert
Description/applicability domain	 R1 = any five membered heterocyclic ring system (the heterocyclic ring can contain any combination of carbon, nitrogen, oxygen or sulphur in which R is connected via a carbon atom) R2 = hydrogen, alkyl carbon
Mechanism	Primary heterocyclic amines undergo metabolism to a reactive nitrenium ion (analogous to that for primary aromatic amines). This ion can bind to DNA via an S_N1 mechanism (Enoch et al 2010).
 1. N-hydroxylation 2. O-acetyltransferase nitrenium ion DNA adduct Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

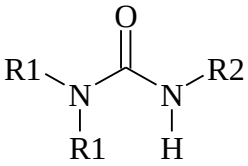
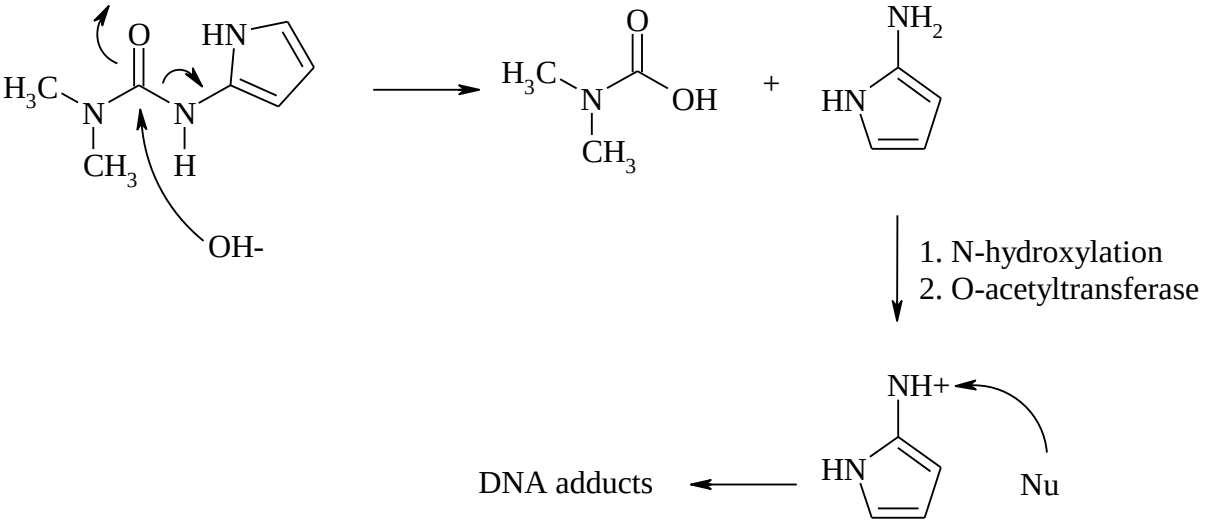
Individual profile/alert	
Name	Protected heterocyclic amines
Type of profile	Structural alert
Description/applicability domain	 R1 = any five membered heterocyclic ring system (the heterocyclic ring can contain any combination of carbon, nitrogen, oxygen or sulphur in which R is connected via a carbon atom) R2 = any combination of methyl, ethyl
Mechanism	Protected secondary and tertiary heterocyclic amines (methyl and ethyl) can potentially undergo metabolism (analogous to that for protected aromatic amines) to a reactive nitrenium ion. This ion can bind to DNA via an S_N1 mechanism (Enoch et al 2010).
 nitrenium ion DNA adduct Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

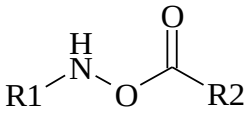
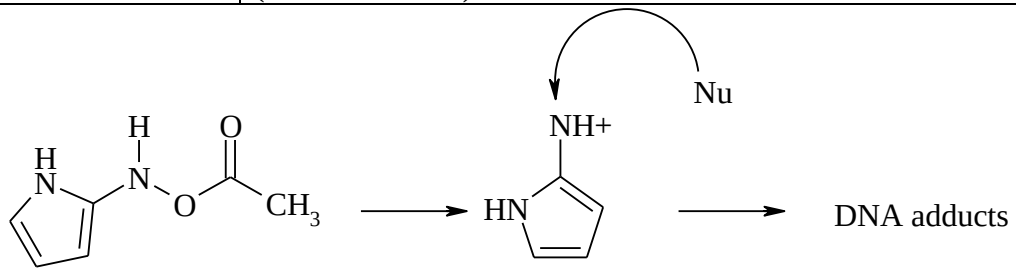
Individual profile/alert	
Name	Heterocyclic nitros
Type of profile	Structural alert
Description/applicability domain	$R-NO_2$ R = any five membered heterocyclic ring system (the heterocyclic ring can contain any combination of carbon, nitrogen, oxygen or sulphur in which R is connected via a carbon atom)
Mechanism	Heterocyclic nitro groups can be metabolised into an *N*-hydroxylated intermediate which subsequently undergoes either acetyl-, phospo- or sulfotransferase. This is an analogous reaction to that which occurs for aromatic nitro chemicals. This species then produces the electrophilic nitrenium ion which is capable of reacting with DNA via an S_N1 mechanism (Enoch et al 2010).
 Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

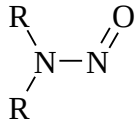
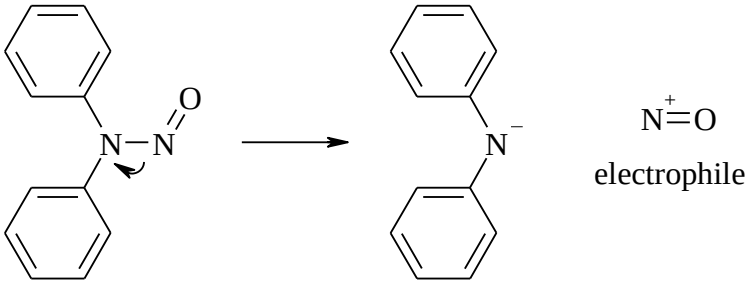
Individual profile/alert	
Name	Heterocyclic nitrosos
Type of profile	Structural alert
Description/applicability domain	R—NO R = any five membered heterocyclic ring system (the heterocyclic ring can contain any combination of carbon, nitrogen, oxygen or sulphur in which R is connected via a carbon atom)
Mechanism	Heterocyclic nitroso compounds have the potential to be reduced, and then hydroxylated to an *N*-hydroxylamine intermediate. This species is then further metabolised by one of three potential transferases, which themselves produce the reactive nitrenium ion which can bind DNA via an S_N1 mechanism (Enoch et al 2010).
 Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

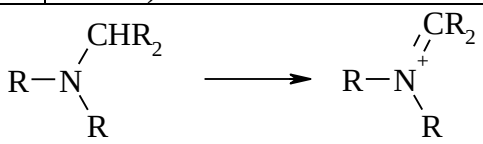
Individual profile/alert	
Name	Heterocyclic *N*-hydroxylamines
Type of profile	Structural alert
Description/applicability domain	 R = any five membered heterocyclic ring system (the heterocyclic ring can contain any combination of carbon, nitrogen, oxygen or sulphur in which R is connected via a carbon atom)
Mechanism	Heterocyclic *N*-hydroxylated groups have the potential to be metabolised by either acetyl-, phospo- or sulfotransferase. These species then produce the electrophilic nitrenium ion which is capable of reacting with DNA via an S_N1 mechanism (Enoch et al 2010).
 O-acetyltransferase (R = $-COCH_3$) (or) phosphotransferase (R = $-PO_3^{2-}$) (or) sulfotransferase (R = $-SO_3^-$) DNA adduct Nitrenium ion Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

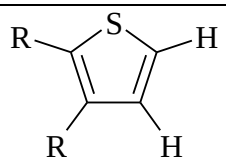
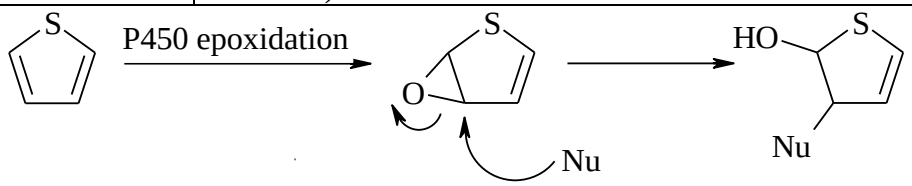
Individual profile/alert	
Name	Heterocyclic azos
Type of profile	Structural alert
Description/applicability domain	R1—N=N—R2 R1 = any five membered heterocyclic ring system (the heterocyclic ring can contain any combination of carbon, nitrogen, oxygen or sulphur in which R is connected via a carbon atom) R2 = any carbon atom, hydrogen
Mechanism	The most likely mechanism is phase one metabolism of the azo via azoreductase producing an heterocyclic amine which then undergoes metabolism into the DNA reactive (via an S_N1 mechanism) nitrenium ion (Enoch et al 2010).
 nitrenium ion  DNA adduct Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

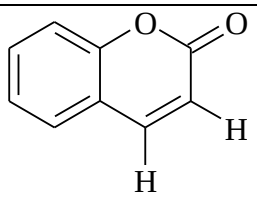
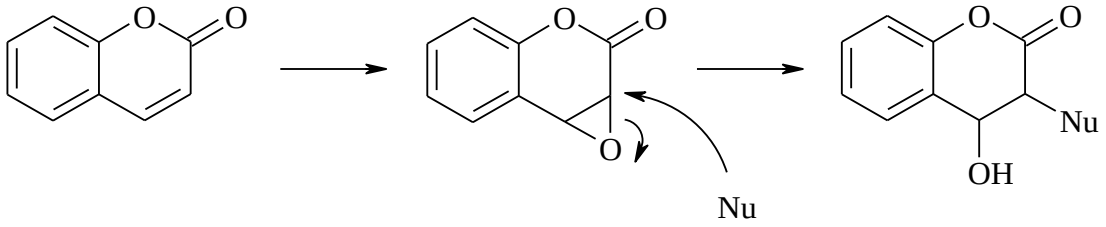
Individual profile/alert	
Name	Heterocyclic phenylureas
Type of profile	Structural alert
Description/applicability domain	 R1 = carbon or hydrogen R2 = any five membered heterocyclic ring system (the heterocyclic ring can contain any combination of carbon, nitrogen, oxygen or sulphur in which R is connected via a carbon atom)
Mechanism	Hydrolysis of the amide bond to produce a heterocyclic amine moiety analogous to the reaction for aromatic system is a possible route to DNA binding for this chemical class. The formation of the nitrenium ion results in DNA binding via an S_N1 mechanism (Enoch et al 2010).
 Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

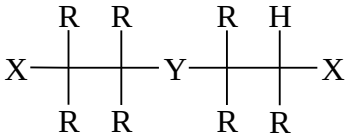
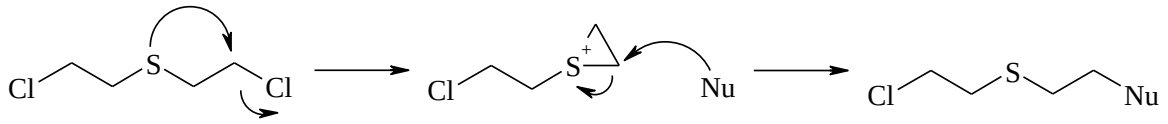
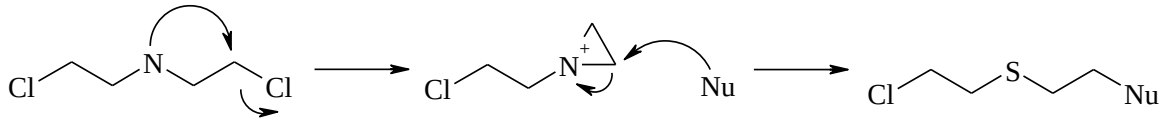
Individual profile/alert	
Name	Ester heterocyclic hydroxylamines
Type of profile	Structural alert
Description/applicability domain	 R1 = any five membered heterocyclic ring system (the heterocyclic ring can contain any combination of carbon, nitrogen, oxygen or sulphur in which R is connected via a carbon atom) R2 = any carbon
Mechanism	Desterification to produce a reactive nitrenium ion capable of reacting with DNA via an S_N1 mechanism is the most likely mechanism. This is a mechanism analogous to that which occurs in for aromatic systems (Enoch et al 2010).
 Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

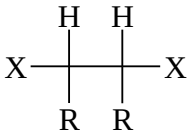
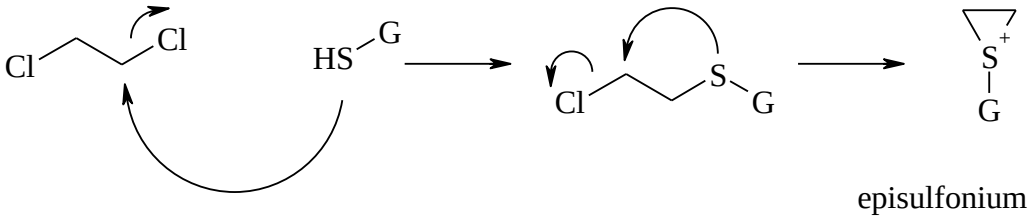
Individual profile/alert	
Name	Nitrosos
Type of profile	Structural alert
Description/applicability domain	 R = aryl carbon (ring system can be aromatic or heteroaromatic)
Mechanism	An S_N1 nitrosation mechanism involving the cleavage of the N-N=O bond has been suggested as a route to DNA binding (Enoch et al 2010).
 electrophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

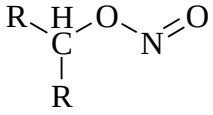
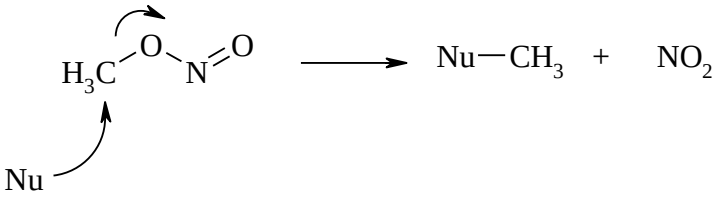
Individual profile/alert	
Name	Aliphatic tertiary amines
Type of profile	Structural alert
Description/applicability domain	 R = aliphatic C The cyclic aliphatic ring system can be any size above n = 3 (i.e. not aziridine). The ring system cannot be heterocyclic
Mechanism	P450 metabolism to a reactive iminium species has been suggested as a potential pathway to DNA adducts via an S_N1 mechanism (Enoch et al 2010).
 iminium ion (electrophile)	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

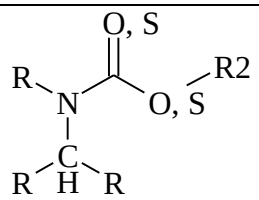
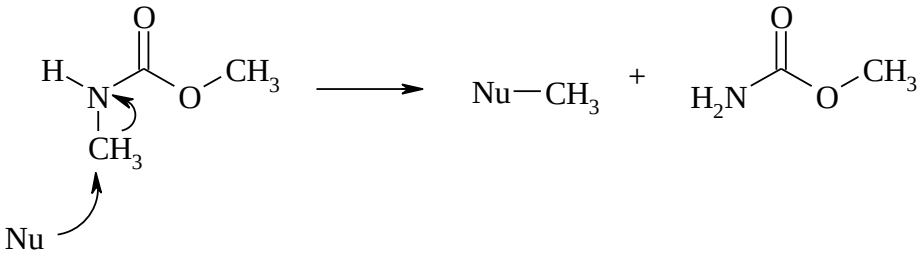
Individual profile/alert	
Name	Thiophenes
Type of profile	Structural alert
Description/applicability domain	 R = hydrogen, any carbon except the following: R ≠ -NHR1 (R1 = any carbon, oxygen, hydrogen), -N(R1)$_2$ (R1 = any combination of methyl or ethyl), -NO$_2$, -NO, -N=NR1 (R1 = any carbon, hydrogen)
Mechanism	An S_N2 mechanism involving P450 epoxidation followed by an ring opening reaction has been suggested to lead to DNA alkylation (Enoch et al 2010).
 Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

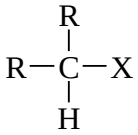
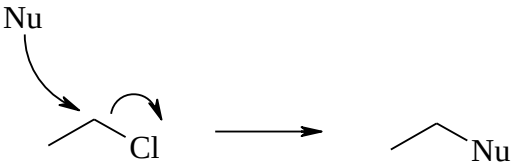
Individual profile/alert	
Name	Coumarins
Type of profile	Structural alert
Description/applicability domain	
Mechanism	Epoxidation to coumarin-3,4-epoxide has been suggested as the primary route of toxicity. The epoxidated species can undergo covalent reaction via an S_N2 mechanism with biological nucleophiles such as DNA (Enoch et al 2010).
 Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

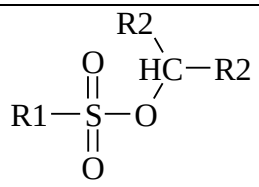
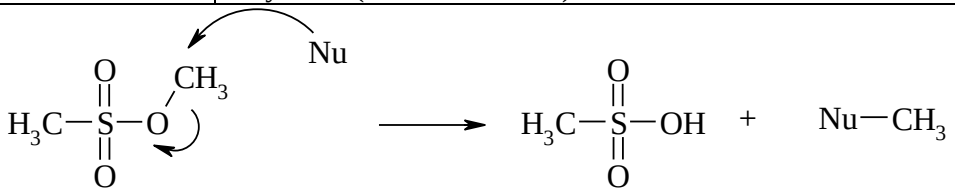
Individual profile/alert	
Name	Mustards
Type of profile	Structural alert
Description/applicability domain	 Y = nitrogen, sulphur (any oxidation state of sulphur is allowed as long as a lone pair remains free for the cyclisation reaction) X = Cl, Br, I R = any carbon, hydrogen
Mechanism	Mustards have been suggested to undergo an intra-molecular cyclisation to form an electrophilic reactive episulfonium ion. The episulfonium ion is then susceptible to S_N2 attack by biological nucleophiles (Enoch et al 2010).
 electrophile: episulfonium ion  electrophile: aziridinium ion DNA adducts Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

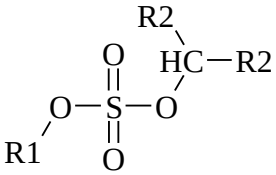
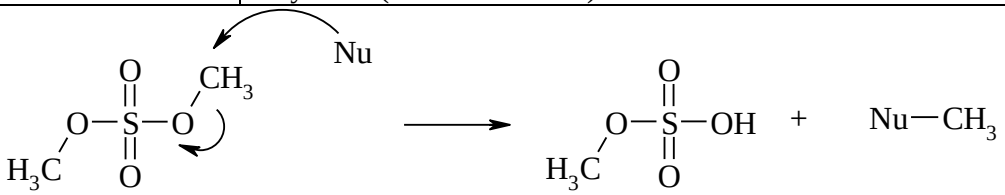
Individual profile/alert	
Name	1,2-Dihaloalkanes
Type of profile	Structural alert
Description/applicability domain	 X = Cl, Br, I R = hydrogen, any carbon
Mechanism	It has been suggested that 1,2-dihaloalkanes undergo an initial attack by glutathione followed by internal cyclisation resulting in the formation of a reactive episulfonium ion. This ion can then undergo an S_N2 type ring opening reaction (Enoch et al 2010).
 episulfonium ion	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

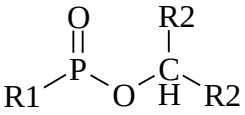
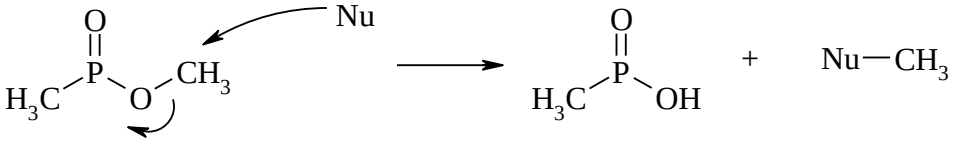
Individual profile/alert	
Name	Alkyl nitrates
Type of profile	Structural alert
Description/applicability domain	 R = any carbon or hydrogen
Mechanism	It has been suggested that a possible mechanism of action is an S_N2 alkylation with the loss of the NO_2 group (Enoch et al 2010).
 Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

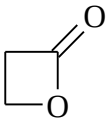
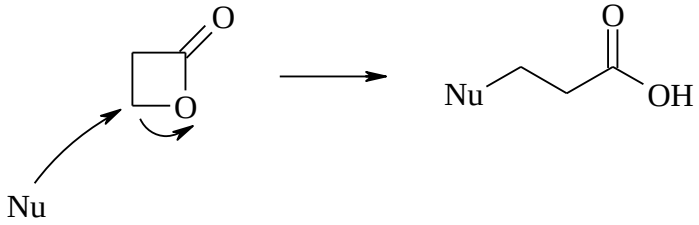
Individual profile/alert	
Name	Alkyl carbamates
Type of profile	Structural alert
Description/applicability domain	 R = any carbon or hydrogen
Mechanism	The most likely mechanism leading to adduct formation has been suggested to be an S_N2 alkylation reaction (Enoch et al 2010).
 Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

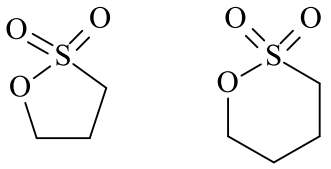
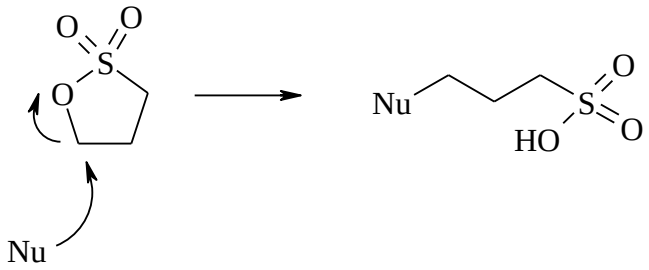
Individual profile/alert	
Name	Aliphatic halides
Type of profile	Structural alert
Description/applicability domain	 R = hydrogen, any carbon except the following: R ≠ carbonyl (these chemicals fall under the α-halocarbonyl alert) -CS, -CN (these chemicals fall under the mustards alert) X = halogen
Mechanism	An S_N2 mechanism has been proposed as the primary method of DNA alkylation (Enoch et al 2010).
	 Nu = biological nucleophile
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

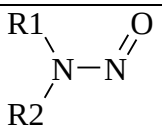
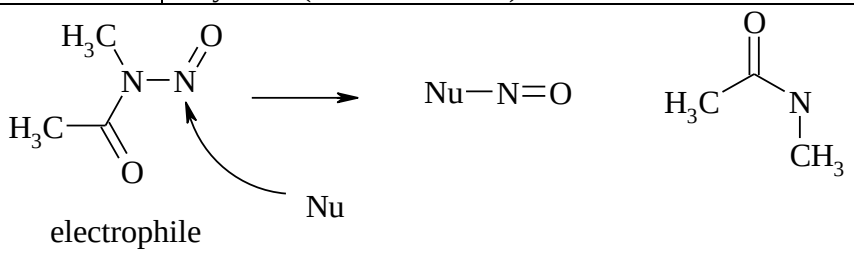
Individual profile/alert	
Name	Sulfonates
Type of profile	Structural alert
Description/applicability domain	 R1 = any carbon R2 = any carbon, hydrogen
Mechanism	An S_N2 mechanism has been proposed as the primary method of DNA alkylation (Enoch et al 2010).
 Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

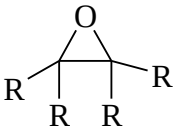
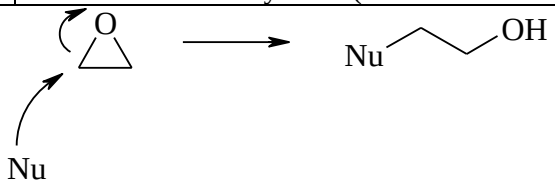
Individual profile/alert	
Name	Sulfates
Type of profile	Structural alert
Description/applicability domain	 R1 = any carbon R2 = any carbon, hydrogen
Mechanism	An S_N2 mechanism has been proposed as the primary method of DNA alkylation (Enoch et al 2010).
 Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

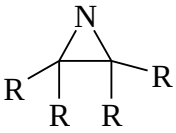
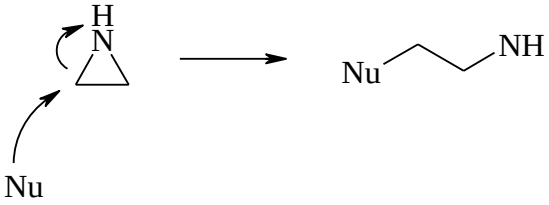
Individual profile/alert	
Name	Phosphonic esters
Type of profile	Structural alert
Description/applicability domain	 R1 = any carbon R2 = any carbon, hydrogen
Mechanism	An S_N2 mechanism has been proposed as the primary method of DNA alkylation (Enoch et al 2010).
 Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

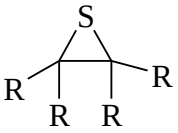
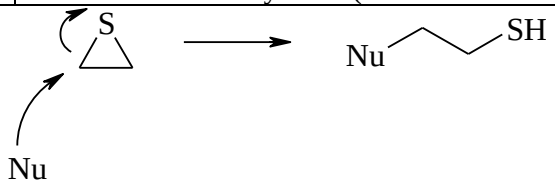
Individual profile/alert	
Name	Lactones
Type of profile	Structural alert
Description/applicability domain	
Mechanism	A ring opening S_N2 mechanism has been proposed as the primary method of DNA alkylation (Enoch et al 2010).
 Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

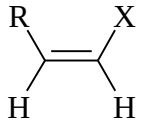
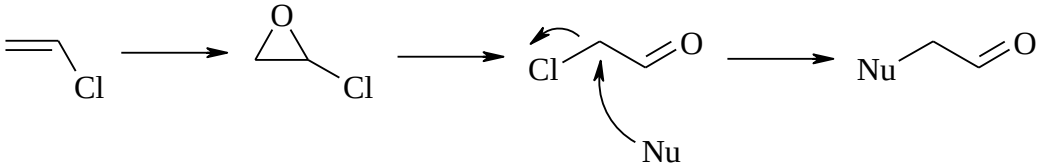
Individual profile/alert	
Name	Sultones
Type of profile	Structural alert
Description/applicability domain	
Mechanism	A ring opening S_N2 mechanism has been proposed as the primary method of DNA alkylation (Enoch et al 2010).
 Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

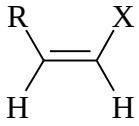
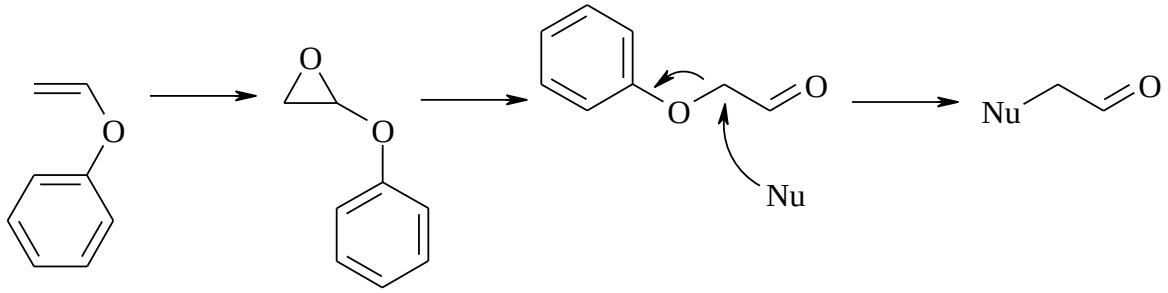
Individual profile/alert	
Name	Nitrosos
Type of profile	Structural alert
Description/applicability domain	 R1 = alkyl carbon R2 = alkyl C, aryl, C=O, C#N, S=O
Mechanism	An S_N2 mechanism has been proposed as the primary method of DNA alkylation (Enoch et al 2010).
 electrophile Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

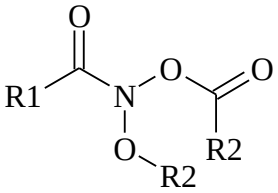
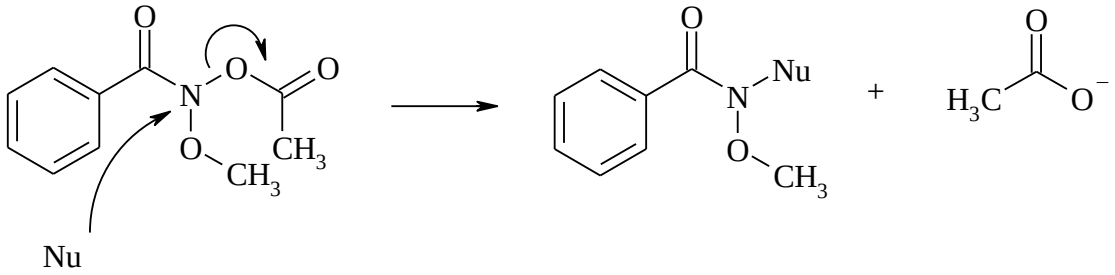
Individual profile/alert	
Name	Epoxides
Type of profile	Structural alert
Description/applicability domain	 R = any carbon, hydrogen
Mechanism	A ring opening S_N2 mechanism has been proposed as the primary method of DNA alkylation (Enoch et al 2010).
 Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

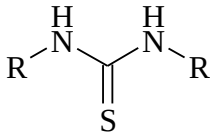
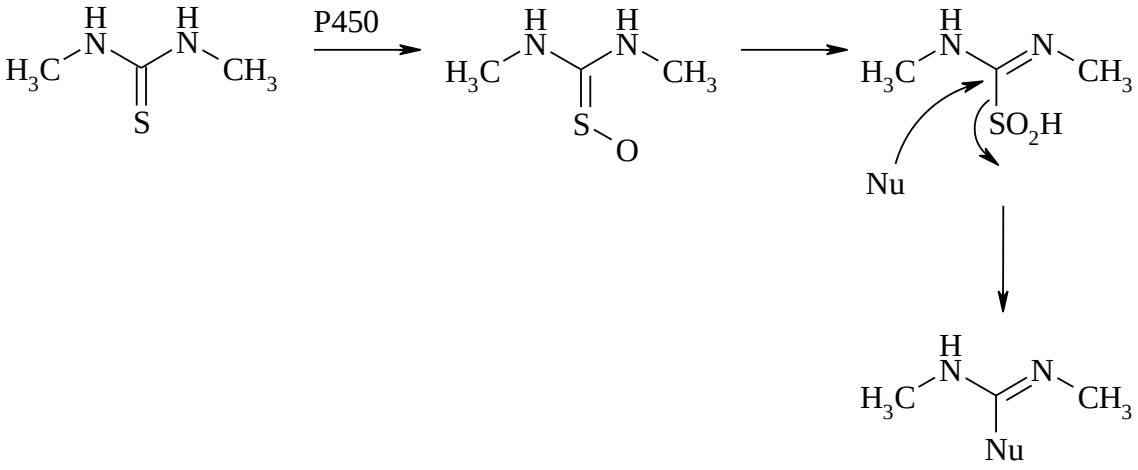
Individual profile/alert	
Name	Aziridines
Type of profile	Structural alert
Description/applicability domain	 R = any carbon, hydrogen
Mechanism	A ring opening S_N2 mechanism has been proposed as the primary method of DNA alkylation (Enoch et al 2010).
 Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

Individual profile/alert	
Name	Sulfuranes
Type of profile	Structural alert
Description/applicability domain	 R = any carbon, hydrogen
Mechanism	A ring opening S_N2 mechanism has been proposed as the primary method of DNA alkylation (Enoch et al 2010).
	 Nu = biological nucleophile
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

Individual profile/alert	
Name	Halogenated polarised alkenes (S_N2)
Type of profile	Structural alert
Description/applicability domain	 R = any carbon, hydrogen, halogen X = F, Cl, Br, I
Mechanism	It has been suggested that monohalo alkenes are metabolised by CYP P450 initially into epoxides. These chemical can either directly bind to DNA or can undergo rapid rearrangement to an equally DNA reactive polarised aldehyde (binding via an S_N2 mechanism) (Enoch et al 2010).
 Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

Individual profile/alert	
Name	Phenoxy polarised alkenes (S_N2)
Type of profile	Structural alert
Description/applicability domain	 R = any carbon, hydrogen, halogen X = Oaryl
Mechanism	It has been suggested that phenoxy alkenes are metabolised by CYP P450 initially into epoxides. These chemical can either directly bind to DNA or can undergo rapid rearrangement to an equally DNA reactive polarised aldehyde (binding via an S_N2 mechanism) (Enoch et al 2010).
 Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

Individual profile/alert	
Name	*N*-acyloxy-*N*-alkoxyamides
Type of profile	Structural alert
Description/applicability domain	 R1 = aromatic R2 = any carbon
Mechanism	An S_N2 mechanism has been suggested to be responsible for the alkylation of DNA (Enoch et al 2010).
 Nu = biological nucleophile	
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

Individual profile/alert	
Name	Thioureas
Type of profile	Structural alert
Description/applicability domain	 R = any carbon, hydrogen
Mechanism	Thioureas have been suggested to be sulfoxidated by P450 resulting in the production of electrophilic sulfinic acids. These species are capable of reacting with biological nucleophiles via an S_N2 type mechanism (Enoch et al 2010).
	 Nu = biological nucleophile
Set of chemicals used for profile development	N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.
Data/Knowledge used for profile development	An extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748