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	Q
domain	
	RX
	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).
	H ₃ C Cl H ₃ C Nu
	Nu
	Nu = biological nucleophile
Set of chemicals used for	N/A – all structural alerts in this profiler were developed from a
profile development	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	An extensive review of the literature was performed enabling the
for profile development	chemistry associated with covalent binding to DNA to be defined and
	encoded in this profiler.
Performance of the	N/A – all alerts in this profiler were developed from a review of the
the profile (for each	chemistry associated with covalent DNA binding. Individual
and point for the	alerts within this profiler
endpoint specific	actes within this promet.
profilers)	
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	$R \xrightarrow{N} X$ R
	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).
H_3C N Cl $-$	$\rightarrow \begin{array}{c} H_{3}C \\ N \\ H_{3}C \\ H_{3}C \\ Nu \end{array} \xrightarrow{O} \begin{array}{c} \\ H_{3}C \\ Nu \end{array} \xrightarrow{O} \begin{array}{c} \\ H_{3}C \\ CH_{3} \\ CH_{3} \end{array} \xrightarrow{O} \begin{array}{c} \\ \\ H_{3}C \\ CH_{3} \\ CH_{3} \end{array} \xrightarrow{O} \begin{array}{c} \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\$
Nu	
	Nu = biological nucleophile
Set of chemicals used for	N/A – all structural alerts in this profiler were developed from a
profile development	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
Data/Knowladge used	An extensive review of the literature was performed enabling the
for profile development	An extensive review of the interature was performed enabling the chamistry associated with covalent hinding to DNA to be defined and
for prome development	encoded in this profiler.
Performance of the	N/A – all alerts in this profiler were developed from a review of the
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual
the profile (for each	toxicological datasets were not analysed during the development of the
endpoint for the	alerts within this profiler.
endpoint specific	1
profilers)	
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

	Individual profile/alert	
Name	Isocyanates	
Type of profile	Structural alert	
Description/applicability	R-N=C=O	
domain	$\mathbf{R} = $ any carbon, hydrogen	
Mechanism	An acylation mechanism has been suggested as being responsible for	
	the formation of DNA adducts (Enoch et al 2010).	
R-N=C=O	$\xrightarrow{OH} R_{N} Nu \xrightarrow{R_{N}} R_{Nu}$	
Nu		
	Nu = biological nucleophile	
Set of chemicals used for	N/A - all structural alerts in this profiler were developed from a	
profile development	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	An extensive review of the literature was performed enabling the	
for profile development	chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.	
Performance of the	N/A – all alerts in this profiler were developed from a review of the	
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual	
the profile (for each	toxicological datasets were not analysed during the development of the	
endpoint for the	alerts within this profiler.	
endpoint specific	^	
profilers)		
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748	

	Individual profile/alert	
Name	Isothiocyanates	
Type of profile	Structural alert	
Description/applicability	R-N=C=S	
domain	R = any carbon, hydrogen	
Mechanism	An acylation mechanism has been suggested as being responsible for	
	the formation of DNA adducts (Enoch et al 2010).	
R-N=C=S	$ \xrightarrow{R_{N}} Nu \xrightarrow{R_{N}} R_{Nu} \xrightarrow{Nu} Nu $	
Nu = biological nucleophile		
Set of chemicals used for	N/A – all structural alerts in this profiler were developed from a	
profile development	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	An extensive review of the literature was performed enabling the	
for profile development	chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.	
Performance of the	N/A – all alerts in this profiler were developed from a review of the	
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual	
the profile (for each	toxicological datasets were not analysed during the development of the	
endpoint for the	alerts within this profiler.	
endpoint specific		
profilers)		
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	
	<u> </u>
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).
$O \xrightarrow{H} O P450$ S	sulfoxidation O H N O H $N=C=O$ O $N=C=O$ O Nu Nu HO S Nu Nu HO S Nu Nu
	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	An extensive review of the literature was performed enabling the
for profile development	chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the	N/A – all alerts in this profiler were developed from a review of the
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual
the profile (for each	toxicological datasets were not analysed during the development of the
endpoint for the	alerts within this profiler.
endpoint specific	
promers)	
Keferences	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

Name Formamides Type of profile Structural alert Description/applicability H domain H R N H N O R = any carbon, hydrogen Mechanism Formamides have been suggested to be metabolised by P450 intreactive isocyanate species. Isocyanates have been shown to be able to accurate the provement of the prove	
Type of profileStructural alertDescription/applicability domain H R H OR = any carbon, hydrogenMechanismFormamides have been suggested to be metabolised by P450 intreactive isocyanate species. Isocyanates have been shown to be able to accurately bind to DNA via an acculation mechanism (Enoch et al.)	
Description/applicability domainH R $R = any carbon, hydrogenMechanismFormamides have been suggested to be metabolised by P450 intreactive isocyanate species. Isocyanates have been shown to be able to accurately bind to DNA via an acculation mechanism (Enoch et al.)$	
R = any carbon, hydrogen Mechanism Formamides have been suggested to be metabolised by P450 intreactive isocyanate species. Isocyanates have been shown to be able to covalently bind to DNA via an actuation mechanism (Enoch at a covalently bind to DNA via at	
Mechanism Formamides have been suggested to be metabolised by P450 intreactive isocyanate species. Isocyanates have been shown to be able t	
2010).	
$H_{3}C \xrightarrow{H} H_{3}C \xrightarrow{N} H_{3$	
- Nu	
Nu = biological nucleophile	
Set of chemicals used for N/A – all structural alerts in this profiler were developed from	
profile development review of the electrophilic chemistry associated with covalent DNA	
the chemistry for endpoints where covalent binding to DNA is the molecular initiating event.	
Data/Knowledge used for profile developmentAn extensive review of the literature was performed enabling the chemistry associated with covalent binding to DNA to be defined an encoded in this profiler.	
Performance of the N/A – all alerts in this profiler were developed from a review of the	
profile / or Analysis of chemistry associated with covalent DNA binding. Individua	
the profile (for each toxicological datasets were not analysed during the development of the	
endpoint for the alerts within this profiler.	
endpoint specific profilers)	
References Enoch et al (2010) Critical Reviews in Toxicology 40 p728-74	

	Individual profile/alert	
Name	Sulfonylureas	
Type of profile	Structural alert	
Description/applicability domain	$ \begin{array}{cccccccccc} & O & H & H \\ & & N & N & N \\ & & N &$	
	$\mathbf{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).	
$\begin{array}{c} O & H & H \\ & & N \\ H_3 C & & N \\ & & O & O \end{array}$	$\sim_{CH_3} \longrightarrow H_3C - \underset{O}{\overset{ }{\overset{ }}{\overset{ }{\overset{ }}{\overset{ }{\overset{ }{\overset{ }{\overset{ }{\overset{ }{\overset{ }{\overset{ }{\overset{ }{\overset{ }{\overset{ }}{\overset{ }}}}}}}}$	
	Nu	
H ₃ C Nu		
	Nu = biological nucleophile	
Set of chemicals used for	N/A - all structural alerts in this profiler were developed from a	
profile development	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	N/A - all alerts in this profiler were developed from a review of the	
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual	
the profile (for each	toxicological datasets were not analysed during the development of the	
endpoint for the	alerts within this profiler.	
endpoint specific profilers)		
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	NH ₂
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).
NH ₂	$ \xrightarrow{N=C=0} \xrightarrow{N}_{H} \xrightarrow{N}_{Nu} $
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	X
domain	
	R´H`X
	$\mathbf{R} = any carbon$
	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).
Cl	
H ₃ C Br H	H_3C Br H_3C Cl H_3C Nu
5	\int
	Nu
	Nu = biological nucleophile
Set of chemicals used for	N/A – all structural alerts in this profiler were developed from a
profile development	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	An extensive review of the literature was performed enabling the
for profile development	chemistry associated with covalent binding to DNA to be defined and
	encoded in this profiler.
Performance of the	N/A – all alerts in this profiler were developed from a review of the
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual
the profile (for each	toxicological datasets were not analysed during the development of the
endpoint for the	alerts within this profiler.
endpoint specific	
profilers)	
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	R1 R1
domain	
	H H R1 H
	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).
нс С	
H ₃ C 0.	$H_3C \longrightarrow H_3C \longrightarrow $
1	
Н	Nu H Nu H
Nu	
	Nu
	-H.O
	120
	•
	H ₃ C Nu
	Nu H
	Nu = biological nucleophile
Set of chemicals used for	N/A – all structural alerts in this profiler were developed from a
profile development	review of the electrophilic chemistry associated with covalent DNA
Prome de l'elopment	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	An extensive review of the literature was performed enabling the
profile development	chemistry associated with covalent binding to DNA to be defined and
F	encoded in this profiler.
Performance of the profile /	N/A – all alerts in this profiler were developed from a review of the
or Analysis of the profile	chemistry associated with covalent DNA binding. Individual
(for each endpoint for the	toxicological datasets were not analysed during the development of
endpoint specific profilers)	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	R1 R1
domain	
	H R2 R1 R2
	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).
H_3C H_3C H_3C O	
	\rightarrow \rightarrow γ
/ сн	I_2 Nu CH Nu CH
	5 1 1 1 1 1 1 3 5
Nu	
	Nu = biological nucleophile
Set of chemicals used for	N/A – all structural alerts in this profiler were developed from a
profile development	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	An extensive review of the literature was performed enabling the
for profile development	chemistry associated with covalent binding to DNA to be defined and
	encoded in this profiler.
Performance of the	N/A – all alerts in this profiler were developed from a review of the
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual
the profile (for each	toxicological datasets were not analysed during the development of the
endpoint for the	alerts within this profiler.
endpoint specific	
profilers)	
Keferences	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	R1 R1
	R1 O H O
	R2 $R2$ $R2$
	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).
H_3C O $R1$ $O^ H_3C$ O	
1	
	CH, Nu O Nu O CH, CH,
Nu	5 CH ₃ 5
	Nu = biological nucleophile
Set of chemicals used for	N/A - all structural alerts in this profiler were developed from a
profile development	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	An extensive review of the literature was performed enabling the
for profile development	chemistry associated with covalent binding to DNA to be defined and
	encoded in this profiler.
Performance of the	N/A – all alerts in this profiler were developed from a review of the
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual
the profile (for each	toxicological datasets were not analysed during the development of the
endpoint for the	alerts within this profiler.
endpoint specific	
profilers)	
Keferences	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	R1 R1
domain	
	$\mathbf{H} \mathbf{N}\mathbf{K}_2$ $\mathbf{K} \mathbf{I} \mathbf{N}\mathbf{K}_2$
	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 , p-unsaturated amides to alkylate DNA (Enoch et al. 2010)
	2010).
H ₃ C	H_3C $O^ H_3C$ O^-
1	
NH	L ₂ Nu NH ₂ Nu NH ₂
	- 2 -
Nu	
	Nu = biological nucleophile
Set of chemicals used for	N/A – all structural alerts in this profiler were developed from a
profile development	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
Data/Knowladge used	Molecular initiating event.
for profile development	chemistry associated with covalent binding to DNA to be defined and
for prome development	encoded in this profiler
Performance of the	N/A – all alerts in this profiler were developed from a review of the
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual
the profile (for each	toxicological datasets were not analysed during the development of the
endpoint for the	alerts within this profiler.
endpoint specific	
profilers)	
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

Individual profile/alert	
Name	Quinones
Type of profile	Structural alert
Description/applicability	Q Q
domain	
	н н
	0
Mechanism	A Michael addition mechanism has been suggested result in a range of
	DNA adducts (Enoch et al 2010).
1	u+
	11
	ОН О
l II-	
	\longrightarrow $\left[\right] \longrightarrow$ $\left[\right]$
\downarrow	Y Nu Y Nu
l – – – – – – – – – – – – – – – – – – –	$\overset{ }{\mathrm{O}}$ $\overset{ }{\mathrm{O}}$
	Nu
	enol keto
	Nu = biological nucleophile
Set of chemicals used for	N/A – all structural alerts in this profiler were developed from a
profile development	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	An extensive review of the literature was performed enabling the
for profile development	chemistry associated with covalent binding to DNA to be defined and
	encoded in this profiler.
Performance of the	N/A – all alerts in this profiler were developed from a review of the
profile / or Analysis of the profile (for each	cnemistry associated with covalent DNA binding. Individual
and point for the	alerts within this profiler
enupoint ior the	
nrofilers)	
References	Enoch et al (2010) Critical Reviews in Toxicology 40 p728-748
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Individual profile/alert	
Name	Quinone-methides
Type of profile	Structural alert
Description/applicability	Q Q
domain	
	H
	H
Mechanism	A Michael addition mechanism has been suggested result in a range of
	DNA adducts (Enoch et al 2010).
	H^{+}
	A
	O OH
/	Nu Nu
Nu	
	Nu = biological nucleophile
Set of chemicals used for	N/A – all structural alerts in this profiler were developed from a
profile development	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	An extensive review of the literature was performed enabling the
for profile development	chemistry associated with covalent binding to DNA to be defined and
	encoded in this profiler.
Performance of the	N/A – all alerts in this profiler were developed from a review of the
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual
the profile (for each	toxicological datasets were not analysed during the development of the
endpoint for the	alerts within this profiler.
endpoint specific	
profilers)	
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

Individual profile/alert	
Name	Hydroquinones
Type of profile	Structural alert
Description/applicability	QR QR
domain	
	OR
	$\mathbf{R} = \mathbf{hydrogen}, \mathbf{methyl}$
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).
	H^+
OH	О / ОН
	\longrightarrow $\ $ \langle $\ $ \longrightarrow $\ $ $ $
ÓH	\tilde{O} $N_{\rm H}$ \tilde{O}
	Nu – biological nucleophile
Set of chemicals used for	N/A – all structural alerts in this profiler were developed from a
profile development	review of the electrophilic chemistry associated with covalent DNA
prome de veropment	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	An extensive review of the literature was performed enabling the
for profile development	chemistry associated with covalent binding to DNA to be defined and
	encoded in this profiler.
Performance of the	N/A – all alerts in this profiler were developed from a review of the
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual
the profile (for each	toxicological datasets were not analysed during the development of the
endpoint for the	alerts within this profiler.
endpoint specific	
profilers)	
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

Individual profile/alert		
Name	Hydroquinones	
Type of profile	Structural alert	
Description/applicability	OH OH R	
domain		
	CH ₂	
	R	
	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).	
H^+		
	▶	
OF OF	H O / OH	
$ \qquad \qquad \longleftarrow \qquad \qquad \bigcirc \qquad \qquad \qquad \qquad \qquad \qquad \qquad \qquad \qquad \qquad \qquad \qquad \qquad \qquad \qquad$		
)	
	i Nu	
	- Nu	
	Nu = biological nucleophile	
Set of chemicals used for	N/A – all structural alerts in this profiler were developed from a	
profile development	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	
Data/We availad as used	Molecular initiating event.	
for profile development	An extensive review of the interature was performed enabling the chamistry associated with covalent binding to DNA to be defined and	
for prome development	encoded in this profiler	
Performance of the	N/A – all alerts in this profiler were developed from a review of the	
nrofile / or Analysis of	chemistry associated with covalent DNA hinding Individual	
the profile (for each	toxicological datasets were not analysed during the development of the	
endpoint for the	alerts within this profiler.	
endpoint specific	r r r	
profilers)		
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
	metabolised into guinones which are canable of DNA hinding via
	Michael addition (Enoch et al 2010)
	P450
	N N
	Nu
	Nu = biological nucleophile
Set of chemicals used for	N/A – all structural alerts in this profiler were developed from a
profile development	review of the electrophilic chemistry associated with covalent DNA binding rather than an analysis of toxical original data. The electro define
	the chemistry for endpoints where covalent hinding to DNA is the
	molecular initiating event
Data/Knowledge used	An extensive review of the literature was performed enabling the
for profile development	chemistry associated with covalent binding to DNA to be defined and
1 1	encoded in this profiler.
Performance of the	N/A – all alerts in this profiler were developed from a review of the
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual
the profile (for each	toxicological datasets were not analysed during the development of the
endpoint for the	alerts within this profiler.
endpoint specific	
profilers)	$\mathbf{E}_{n} = 1 + 1 + (2010) \mathbf{C}_{n} = 1 \mathbf{D}_{n-1} = 1 1 1 = 1 1 1 = 1 1 1 1 = 1 1 1 = 1 $
Keferences	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

	Individual profile/alert
Name	Arenes
Type of profile	Structural alert
Description/applicability	Ŗ
domain	
	R
	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).
$\left[\begin{array}{c} 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 $	
	\sim
	Nu
	Nu = biological nucleophile
Set of chemicals used for	N/A – all structural alerts in this profiler were developed from a
profile development	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	An extensive review of the literature was performed enabling the
for profile development	chemistry associated with covalent binding to DNA to be defined and
Doufourne on oo of the	encoded in this profiler.
Performance of the	N/A – all alerts in this profiler were developed from a review of the
the profile (for each	toxicological datasets were not analysed during the development of the
and point for the	alerts within this profiler
enupoint for the	alerts within this promet.
nrofilers)	
References	Enoch et al (2010) Critical Reviews in Toxicology 40 p728-748
	Enoch et al (2010) Chucai Reviews in Toxicology, 40, p/20-746

	Individual profile/alert	
Name	Polycyclic (PAHs) and heterocyclic (HACs) aromatic hydrocarbons	
Type of profile	Structural alert	
Description/applicability	Н	
domain		
	H	
	H	
	(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	
	50 Ovidation	
	人人人/ 人人人/	
	HO, \uparrow \sim \sim 0, \downarrow \sim \sim	
	OH Ö	
	electrophile	
	Nu V	
	0	
	DNA adduct	
	Nu = biological nucleophile	
Set of chemicals used for	N/A – all structural alerts in this profiler were developed from a	
profile development	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	An extensive review of the literature was performed enabling the	
for profile development	chemistry associated with covalent binding to DNA to be defined and	
	encoded in this profiler.	
Performance of the	N/A - all alerts in this profiler were developed from a review of the	
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual	
the profile (for each	toxicological datasets were not analysed during the development of the	
endpoint for the	alerts within this profiler.	
endpoint specific		
profilers)		
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	$ \begin{array}{c} R1 \\ O \\ H \\ R2 \end{array} $
	$R_1 = Methyl, Hydrogen$ $R_2 = any carbon bydrogen$
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).
CH ₃ O CH ₃ CH ₃	$\begin{array}{c} P450 \\ \hline \\ P450 \\ \hline \\ \\ P450 \\ \hline \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ $
Set of chemicals used for	Nu = biological nucleophile N/A – all structural alerts in this profiler were developed from a
profile development	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) References	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.
	Enoth et al (2010) Chucal Reviews III 10XIC010gy, 40 , $p/26-746$

	Individual profile/alert	
Name	3-Methylindole derivatives	
Type of profile	Structural alert	
Description/applicability	CH ₃	
domain		
Mechanism	P450 dehydrogenation results in an imine-methide intermediate	
	capable of undergoing Michael addition with biological nucleophiles	
	(Enoch et al 2010).	
CII	Su -Nu	
CH ₃	$\frac{CH_2}{1}$	
P450		
	$\rightarrow \parallel \mid \rangle \qquad / \xrightarrow{1 \leftarrow 1} \parallel \mid \rangle$	
N		
Ĥ		
	H	
	[B]	
	٧	
	CH ₃	
	INU	
	W N H	
Sat of chamicals used for	N(A) = 01010gical nucleophile	
nofile development	$1\sqrt{A}$ – an structural alerts in this promet were developed from a review of the electrophilic chemistry associated with covalent DNA	
prome de velopment	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	An extensive review of the literature was performed enabling the	
for profile development	chemistry associated with covalent binding to DNA to be defined and	
	encoded in this profiler.	
Performance of the	N/A - all alerts in this profiler were developed from a review of the	
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual	
the profile (for each	toxicological datasets were not analysed during the development of the	
endpoint for the	alerts within this profiler.	
endpoint specific		
profilers)	Enach et al (2010) Critical Devices in Terries Level 40, 700 740	
Keterences	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748	

Individual profile/alert	
Name	Furans
Type of profile	Structural alert
Description/applicability	$\mathbf{p} \neq 0 \mathbf{p}$
domain	
	R = hydrogen, any carbon expect the following
	$R \neq$ -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).
	H^+
0	
	Nu
	Nu
	Nu = biological nucleophile
Set of chemicals used for	N/A – all structural alerts in this profiler were developed from a
profile development	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	An extensive review of the literature was performed enabling the
for profile development	chemistry associated with covalent binding to DNA to be defined and
	encoded in this profiler.
Performance of the	N/A – all alerts in this profiler were developed from a review of the
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual
the profile (for each	toxicological datasets were not analysed during the development of the
endpoint for the	alerts within this profiler.
endpoint specific	-
profilers)	
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

Individual profile/alert	
Name	Thiophenes
Type of profile	Structural alert
Description/applicability	R S H
domain	
	K K
	R = hydrogen, any carbon expect the following
	$R \neq$ -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).
	$\overline{0}$
\sim P450 su	lfoxidation S Nu
	Nu
	Nu = biological nucleophile
Set of chemicals used for	N/A – all structural alerts in this profiler were developed from a
profile development	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	An extensive review of the literature was performed enabling the
for profile development	chemistry associated with covalent binding to DNA to be defined and
	encoded in this profiler.
Performance of the	N/A – all alerts in this profiler were developed from a review of the
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual
the profile (for each	toxicological datasets were not analysed during the development of the
endpoint for the	alerts within this profiler.
endpoint specific	
profilers)	
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	0
domain	
	R
	$\mathbf{R} = any carbon, hydrogen$
Mechanism	Mono aldehydes undergo Schiff base formation (Enoch et al 2010).
	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$
	R^{-1}
	R = DNA chain
Set of chemicals used for	N/A - all structural alerts in this profiler were developed from a
profile development	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	An extensive review of the literature was performed enabling the
for profile development	encoded in this profiler.
Performance of the	N/A – all alerts in this profiler were developed from a review of the
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual
the profile (for each	toxicological datasets were not analysed during the development of the
endpoint for the	alerts within this profiler.
endpoint specific	
profilers)	
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	Ö
domain	D
	R
	0
	R = any carbon, hydrogen
Mechanism	A multi-step Schiff base mechanism leads to cross-linking of DNA
	chains (Enoch et al 2010).
	R
),	0 ,0 ,N
	но но
0 1	N [×] NH ₂ N [×]
	\mathbf{R} \mathbf{R} \mathbf{R}
	K K
NH ₂	
K	
	R = DNA chain
Set of chemicals used for	N/A – all structural alerts in this profiler were developed from a
profile development	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
Data/Knowledge used	An extensive review of the literature was performed enabling the
for profile development	chemistry associated with covalent hinding to DNA to be defined and
for prome development	encoded in this profiler
Performance of the	N/A – all alerts in this profiler were developed from a review of the
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual
the profile (for each	toxicological datasets were not analysed during the development of the
endpoint for the	alerts within this profiler.
endpoint specific	L L
profilers)	
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

Individual profile/alert	
Name	<i>N</i> -methylol derivatives
Type of profile	Structural alert
Description/applicability	R ₂ N-C-OH
domain	- H ₂
	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).
H ₃ C ^{-N} -OH	$\longrightarrow H_{3}C^{-NH_{2}} \qquad \underbrace{\bigwedge_{H}^{O}}_{H} \qquad \underbrace{\bigwedge_{H}^{N}}_{H} \stackrel{M}{\longrightarrow} \underbrace{\bigwedge_{H}^{N}}_{H}$
	NUL
dR = deoxyribose phosphate fragment dR	
Set of chemicals used for	N/A – all structural alerts in this profiler were developed from a
profile development	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	An extensive review of the literature was performed enabling the
for profile development	chemistry associated with covalent binding to DNA to be defined and
	encoded in this profiler.
Performance of the	N/A – all alerts in this profiler were developed from a review of the
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual
and point for the	solution of the state of the st
enupoint for the	alerts wrunn uns promer.
nrofilers)	
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

Individual profile/alert	
Name	Thiazoles
Type of profile	Structural alert
Description/applicability	H. S
domain	
	N = N
	П
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).
$H \xrightarrow{S} R \xrightarrow{R} P450 \text{ epoxidation} \qquad H \xrightarrow{S} R \xrightarrow{R} HO \xrightarrow{H} N$	
Nu $H \rightarrow O$ $H \rightarrow O$	
Set of chemicals used for	N/A - all structural alerts in this profiler were developed from a
profile development	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
Data/Knowladge used	An extensive review of the literature was performed anabling the
for profile development	An extensive review of the interature was performed enabling the chemistry associated with covalent binding to DNA to be defined and
for prome development	encoded in this profiler
Performance of the	N/A – all alerts in this profiler were developed from a review of the
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual
the profile (for each	toxicological datasets were not analysed during the development of the
endpoint for the	alerts within this profiler.
endpoint specific	
profilers)	
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

Individual profile/alert	
Name	Benzylamines
Type of profile	Structural alert
Description/applicability	H ₂
domain	$\sim C_{\sim}$
	NH ₂
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).
Nu	
NH	P450 \sim
	$2 \longrightarrow $
Sat of abomicals used for	N/Λ all structural electer in this profiler were developed from a
Set of chemicals used for	N/A – all structural alerts in this promet were developed from a review of the electrophilic chemistry associated with covalent DNA
prome development	hinding 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	An extensive review of the literature was performed enabling the
for profile development	chemistry associated with covalent binding to DNA to be defined and
F	encoded in this profiler.
Performance of the	N/A – all alerts in this profiler were developed from a review of the
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual
the profile (for each	toxicological datasets were not analysed during the development of the
endpoint for the	alerts within this profiler.
endpoint specific	
profilers)	
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-N-NH ₂ H
	R = any atom
Mechanism	Formaldenyde 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).
H ₂ N-NH ₂ H ₂ C	$\stackrel{\bigstar}{=}$ \longrightarrow $H_2C=N-NH_2$ \longrightarrow $H_3C-N=N-OH$
	↓ ↓
	$CH_3 + N_2 H_2O$
	electrophile
Set of chemicals used for	N/A - all structural alerts in this profiler were developed from a
profile development	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	An extensive review of the literature was performed enabling the
for profile development	encoded in this profiler.
Performance of the	N/A – all alerts in this profiler were developed from a review of the
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual
the profile (for each	toxicological datasets were not analysed during the development of the
endpoint for the	alerts within this profiler.
endpoint specific	
profilers)	
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

Individual profile/alert	
Name	Aliphatic <i>N</i> -Nitro
Type of profile	Structural alert
Description/applicability	R O
domain	N-N
	R = CH O
	R
	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_N 1 mechanism (Enoch et al 2010).
H ₃ CO	$H_3C \longrightarrow 0 \qquad H_3C \longrightarrow 0$
N-N+	\rightarrow N-N \rightarrow N-N
¹¹ ₃ C 0	
	CH ₃
	V
	H_2C-C^+ , N , H O \leftarrow $(=0, H_2C)$
	$H C = \frac{N - OH}{N}$
	netrophile n ₃ c netrophile
Set of chemicals used for	N/A – all structural alerts in this profiler were developed from a
profile development	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	An extensive review of the literature was performed enabling the
for profile development	chemistry associated with covalent binding to DNA to be defined and
	encoded in this profiler.
Performance of the	N/A – all alerts in this profiler were developed from a review of the
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual
the profile (for each	toxicological datasets were not analysed during the development of the
endpoint for the	alerts within this profiler.
endpoint specific	
profilers)	
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	$R1 \sim N \sim R2$
	R1 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).
$H_3C_N N_{N_1}CH_3 \longrightarrow N_2 H_3C_N CH_3 CH_3^+$	
ĊH ₃	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	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
endpoint for the endpoint specific	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	$C - N \equiv N$ $C = N = N$	
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).	
$C - N \equiv N \xrightarrow{-N_2} C^- \longrightarrow DNA$ adducts		
\mathbf{H}^+		
	NI	
$C-N \stackrel{+}{\equiv} N \stackrel{-N_2}{\longrightarrow} C^+ \stackrel{-}{\longrightarrow} DNA adducts$		
Set of chemicals used for	N/A - all structural alerts in this profiler were developed from a	
profile development	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	
Data/Knowladga usad	An extensive review of the literature was performed enabling the	
for profile development	chemistry associated with covalent binding to DNA to be defined and	
	encoded in this profiler.	
Performance of the	N/A – all alerts in this profiler were developed from a review of the	
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual	
the profile (for each	toxicological datasets were not analysed during the development of the	
endpoint for the	alerts within this profiler.	
endpoint specific		
profilers)		
Keferences	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	ч
domain	
	H
	H Y Y
	H
	(any C in the above structures can be substituted for N)
Mechanism	Bay region PAHs and HACs undergo P450 mediated oxidation to
Witchamsm	produce a reactive carbenium ion Alkylation then occurs via an Syl
	mechanism (Enoch et al 2010)
^	
	lation P450
	\rightarrow $()$ $()$ $()$ $()$ $()$ $()$ $()$ $()$
	O OH
bay region PAH	
	11.1 D150
	oxidation P450
	*
	HO C^+ \downarrow \downarrow \downarrow \downarrow \downarrow \downarrow \downarrow \downarrow
	$HO' \downarrow \checkmark HO' \downarrow \checkmark$
	electrophile
	Nu = biological nucleophile
Set of chemicals used for	N/A – all structural alerts in this profiler were developed from a
profile development	review of the electrophilic chemistry associated with covalent DNA
r · · · · · · · · ·	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	An extensive review of the literature was performed enabling the
for profile development	chemistry associated with covalent binding to DNA to be defined and
	encoded in this profiler.
Performance of the	N/A - all alerts in this profiler were developed from a review of the
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual
the profile (for each	toxicological datasets were not analysed during the development of the
endpoint for the	alerts within this profiler.
endpoint specific	
profilers)	
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
	R-CH O
	N-N
	K
	R = any carbon or hydrogen
Mechanism	An S_N mechanism has been suggested as a route to DNA hinding. The allud \mathbf{P} aroun conjunction of hydroxylation
	mathelism producing a carbonium ion leading to an S 1
	alkylation reaction (Enoch et al 2010)
$H_{C} \longrightarrow O$ H_{C}	\neg 0
	$N = N$ \longrightarrow $T = 0$ $H_3 C$
НО-	$H_{3}C$ N=N-OH
ĊH,	ĊH ₂
5	5
	♥
	+
	H_3C-C N ₂ H_2O
	electrophile
Set of chemicals used for profile	electrophile N/A – all structural alerts in this profiler were developed from
Set of chemicals used for profile development	electrophile N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with
Set of chemicals used for profile development	electrophile 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
Set of chemicals used for profile development	electrophile 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
Set of chemicals used for profile development	electrophile 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.
Set of chemicals used for profile development Data/Knowledge used for profile	electrophile 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. An extensive review of the literature was performed enabling
Set of chemicals used for profile development Data/Knowledge used for profile development	electrophile 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. 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.
Set of chemicals used for profile development Data/Knowledge used for profile development	electrophile 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. 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.
Set of chemicals used for profile development Data/Knowledge used for profile development Performance of the profile / or Analysis of the profile (for each	electrophile 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. 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. N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent DNA binding
Set of chemicals used for profile development Data/Knowledge used for profile development Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific	electrophile 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. 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. 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
Set of chemicals used for profile development Data/Knowledge used for profile development Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers)	electrophile 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. 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. 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.
Set of chemicals used for profile development Data/Knowledge used for profile development Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers) References	electrophile 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. 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. 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. Enoch et al (2010) Critical Reviews in Toxicology. 40.
Set of chemicals used for profile development Data/Knowledge used for profile development Performance of the profile / or Analysis of the profile (for each endpoint for the endpoint specific profilers) References	electrophile 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. 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. 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. 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	C H ₂
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).
C H ₂	$\xrightarrow{\text{droxylation}} \underset{OH}{\overset{H}{}} \xrightarrow{\text{Sulfation}} \underset{HO_3S}{\overset{H}{}} \xrightarrow{H}$
	H
Sat of abamicals used for	N/A all structural alorts in this profiler were developed from a
Set of chemicals used for	N/A – an structural alerts in this profiler were developed from a
prome development	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	An extensive review of the literature was performed enabling the
for profile development	chemistry associated with covalent binding to DNA to be defined and
	encoded in this profiler.
Performance of the	N/A – all alerts in this profiler were developed from a review of the
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual
the profile (for each	toxicological datasets were not analysed during the development of the
endpoint for the	alerts within this profiler.
endpoint specific	
profilers)	
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	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$
	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).
R R R R R R R R R R	$ \begin{array}{c} \text{oxidation} \\ \text{oxidation} \\ \text{c} \\$
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	An extensive review of the literature was performed enabling the
for profile development	chemistry associated with covalent binding to DNA to be defined and
	encoded in this profiler.
Performance of the	N/A - all alerts in this profiler were developed from a review of the
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual
the profile (for each	toxicological datasets were not analysed during the development of the
endpoint for the	alerts within this profiler.
endpoint specific	
profilers)	
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	S,O X	
domain	R V	
	$\mathbf{R} = any carbon$	
	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).	
0, Cl -	\longrightarrow $Cl^- + 0 > 1^+ > 0 > 1^+$	
	C C	
carbenium ion oxonium ion		
	recommendation destroubile	
	resonance staomsed electrophile	
Set of chemicals used for	N/A – all structural alerts in this profiler were developed from a	
profile development	review of the electrophilic chemistry associated with covalent DNA	
F- 0-11 F	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	An extensive review of the literature was performed enabling the	
for profile development	chemistry associated with covalent binding to DNA to be defined and	
	encoded in this profiler.	
Performance of the	N/A – all alerts in this profiler were developed from a review of the	
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual	
the profile (for each	toxicological datasets were not analysed during the development of the	
endpoint for the	alerts within this profiler.	
endpoint specific		
profilers)		
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	H_{P1-N}
domain	
	R2
	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).
NH ₂ 2. O-ace	droxylation tyltransferase NH+ Nu Nu Nu
primary amine	nitrenium ion DNA adduct
	Nu = biological nucleophile
Set of chemicals used for	N/A - all structural alerts in this profiler were developed from a
profile development	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	An extensive review of the literature was performed enabling the
for profile development	encoded in this profiler
Performance of the	N/A – all alerts in this profiler were developed from a review of the
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual
the profile (for each	toxicological datasets were not analysed during the development of the
endpoint for the	alerts within this profiler.
endpoint specific	
profilers)	
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	,R2
domain	R1-N
	R2
	R1 – any aromatic or betero-aromatic (connected via a carbon atom)
	R_{1} = any aromatic of netro-aromatic (connected via a carbon atom) R_{2} = 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_N 1 mechanism (Enoch et al 2010).
	NH_2 1. N-hydroxylation NH_2
$H_3C_NCH_3$ dealkyla	ation \downarrow 2. O-acetyltransferase \downarrow
	\rightarrow
	Nu
Alkyl amine	primary amine nitrenium ion
	•
	,
	Nu
	HN
	· ·
	DNA adduct
	Nu = biological nucleophile
Set of chemicals used for	N/A - all structural alerts in this profiler were developed from a
profile development	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
Doto/Wnorrlador	Molecular initiating event.
for profile development	All 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	N/A – all alerts in this profiler were developed from a review of the
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual
the profile (for each	toxicological datasets were not analysed during the development of the
endpoint for the	alerts within this profiler.
endpoint specific	
profilers)	
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	R-NO ₂	
domain	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_N 1 mechanism	
	(Enoch et al 2010).	
NO	OH O-acetyltransferase (R = -COCH ₃) (or) OR	
100_2 1. Nitroreductas	be phosphotransferase (R = -PO ₃ ²⁻) (or)	
2. N-hydroxylat	ion sulfotransferase ($\mathbf{R} = -\mathbf{SO}_3^-$)	
	→ ────→	
	Y CONTRACTOR OF CONTRACTOR	
	Nu	
	NU NH NH+	
	L Nu	
	DNA adduct Nitrenium ion	
	Nu = biological nucleophile	
Set of chemicals used for	N/A – all structural alerts in this profiler were developed from a	
profile development	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	An extensive review of the literature was performed enabling the	
for prome development	chemistry associated with covarent binding to DNA to be defined and	
Performance of the	N/A all elerts in this profiler were developed from a review of the	
nrofile / or Analysis of	$\Delta = an area is in uns promer were developed from a review of the chemistry associated with covalent DNA binding Individual$	
the profile (for each	toxicological datasets were not analysed during the development of the	
endpoint for the	alerts within this profiler.	
endpoint specific		
profilers)		
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	R-NO	
domain	\mathbf{R} = any aromatic or hetero-aromatic (connected via a carbon atom)	
Mechanism	Aromatic nitroso compounds are reduced and then hydroxylated to an	
	<i>N</i> -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_N 1	
	mechanism (Enoch et al 2010).	
	OH O-acetyltransferase (R = -COCH ₃) (or) OR	
NO	HN phosphotransferase (R = -PO ₃ ²⁻) (or) HN	
2 N-hydroxylati	sulform sulformsferase ($\mathbf{R} = -\mathbf{SO}_2^{-1}$)	
, v	~ ~ ~	
	٧	
	Nus	
	NH NH+	
	L Nu L	
	DNA adduct Nitrenium ion	
	Nu = biological nucleophile	
Set of chemicals used for	N/A - all structural alerts in this profiler were developed from a	
profile development	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	An extensive review of the literature was performed enabling the	
for profile development	chemistry associated with covalent binding to DNA to be defined and	
	encoded in this profiler.	
reriormance of the	N/A – all alerts in this profiler were developed from a review of the	
the profile (for each	toxicological detects were not analyzed during the development of the	
and prome (10) each	alerts within this profiler	
endpoint specific	alerts within this promet.	
nrofilers)		
References	Enoch et al (2010) Critical Reviews in Toxicology 40, p729, 749	
Nelel ences	1 Enoth et al (2010) Chucai Keviews III Toxicology, 40, p/28-748	

Individual profile/alert	
Name	Aromatic N-hydroxylamines
Type of profile	Structural alert
Description/applicability	OH
domain	R-N
	Н
	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 $S_N 1$ mechanism (Enoch et al 2010).
OH	O-acetyltransferase ($R = -COCH_3$) (or) OR
	phosphotransferase (R = -PO ₃ ²⁻) (or) HIN
	sulfotransferase ($\mathbf{R} = -\mathbf{SO}_{-}$)
	Y
	Nu
	NH NH+
	Nu Nu
	DNA adduct Nitrenium ion
	Nu = biological nucleophile
Set of chemicals used for	N/A – all structural alerts in this profiler were developed from a
profile development	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	An extensive review of the literature was performed enabling the
for profile development	chemistry associated with covalent binding to DNA to be defined and
	encoded in this profiler.
Performance of the	N/A – all alerts in this profiler were developed from a review of the
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual
the profile (for each	toxicological datasets were not analysed during the development of the
enapoint for the	alerts within this promer.
enupoint specific	
Poforoncos	Encel at al (2010) Critical Daviance in Taxicalary 40 - 729 749
References	Enoch et al (2010) Unucal Reviews in Toxicology, 40 , $p/28$ - $/48$

	Individual profile/alert	
Name	Aromatic azos	
Type of profile	Structural alert	
Description/applicability	R1 - N = N - R2	
domain	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_N mechanism) nitrenium ion (Enoch et al 2010).	
	$\frac{\text{NH}_2}{1}$ 1. N-hydroxylation $\frac{\text{NH}_+}{1}$	
	2. O-acetyltransferase	
aromatic azo	primary amine nitrenium ion	
	↓ ↓	
	HN ^{_Nu}	
	DNA adduct	
Set of chemicals used for	N/A = all structural alerts in this profiler were developed from a	
profile development	review of the electrophilic chemistry associated with covalent DNA	
r	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	An extensive review of the literature was performed enabling the	
for prome development	encoded in this profiler	
Performance of the	N/A – all alerts in this profiler were developed from a review of the	
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual	
the profile (for each	toxicological datasets were not analysed during the development of the	
endpoint for the	alerts within this profiler.	
endpoint specific		
profilers)	Enach et al (2010) Critical Devices in Territoria 40, 700 740	
Kelerences	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	$R1 \xrightarrow{V} R2$ $R1 \xrightarrow{V} R2$ $R1 = carbon \text{ or hydrogen}$ $R2 = any aromatic or hetero aromatic (connected via a carbon)$
	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).
H_3C N N H CH_3 H H H	$\rightarrow H_{3}C \underset{CH_{3}}{\overset{O}{\longrightarrow}} OH + \underset{CH_{3}}{\overset{H}{\longrightarrow}} OH$
OH-	1. N-hydroxylation 2. O-acetyltransferase
	DNA adducts
	Nu = biological nucleophile
development	N/A – an structural alerts in this promer 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	An extensive review of the literature was performed enabling
development	the chemistry associated with covalent binding to DNA to be defined and encoded in this profiler.
Performance of the profile / or	N/A – all alerts in this profiler were developed from a review
Analysis of the profile (for each	of the chemistry associated with covalent DNA binding.
endpoint for the endpoint specific	Individual toxicological datasets were not analysed during the
profilers)	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	0	
domain		
	$R1^{1}O^{R2}$	
	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).	
	V Nu	
	NH+	
	\downarrow	
	$CH_3 \longrightarrow DNA$ adducts	
	Nu –	
	hiological nucleonhile	
Set of chemicals used for	N/A – all structural alerts in this profiler were developed from a	
profile development	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	An extensive review of the literature was performed enabling the	
for profile development	chemistry associated with covalent binding to DNA to be defined and	
	encoded in this profiler.	
Performance of the	N/A – all alerts in this profiler were developed from a review of the	
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual	
the profile (for each	toxicological datasets were not analysed during the development of the	
endpoint for the	alerts within this profiler.	
endpoint specific		
profilers)		
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	H
domain	RI-N
	R2
	R1 = any five membered heterocyclic ring system (the heterocyclic ring can contain any combination of carbon nitrogen exugen or
	sulphur in which R is connected via a carbon atom)
	$R^2 = hydrogen alkyl carbon$
Mechanism	Primary heterocyclic amines undergo metabolism to a reactive
Witchamsm	nitrenium ion (analogous to that for primary aromatic amines) This
	ion can bind to DNA via an $S_{\rm N1}$ mechanism (Enoch et al 2010).
	_Nu
$\frac{\text{NH}_2}{1. \text{N-hy}}$	rdroxylation NH+ - HN
2. O-ac	etyltransferase
H_3C_N	$\xrightarrow{\cdot} H_3C_N \longrightarrow H_3C_N \longrightarrow$
	Nu
	nitrenium ion DNA adduct
	Nu = biological nucleophile
Set of chemicals used for	N/A – all structural alerts in this profiler were developed from a
profile development	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	An extensive review of the literature was performed enabling the
for profile development	chemistry associated with covalent binding to DNA to be defined and
	encoded in this profiler.
Performance of the	N/A – all alerts in this profiler were developed from a review of the
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual
the profile (for each	toxicological datasets were not analysed during the development of the
endpoint for the	alerts within this profiler.
endpoint specific	
profilers)	
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	$R = NO_2$
domain	\vec{R} – any five membered beterocyclic ring system (the beterocyclic 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 <i>N</i> -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 $S_{\rm N}$ 1
	mechanism (Enoch et al 2010).
NO	OH O-acetyltransferase (R = -COCH ₃) (or) OR
1. Nitroreducta	se phosphotransferase (R = -PO ₃ ²⁻) (or)
2. N-hydroxyla	tion sulfotransferase ($\mathbf{R} = -\mathbf{SO}_3^-$)
	``````````````````````````````````````
	NU NH NH+
	HN HN
	DNA adduct Nitrenium ion
	Nu = biological nucleophile
Set of chemicals used for	N/A – all structural alerts in this profiler were developed from a
profile development	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
Data/Knowladge used	An extensive review of the literature was performed anothing the
for profile development	All extensive review of the interature was performed enabling the chamistry associated with covalent hinding to DNA to be defined and
	encoded in this profiler
Performance of the	N/A – all alerts in this profiler were developed from a review of the
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual
the profile (for each	toxicological datasets were not analysed during the development of the
endpoint for the	alerts within this profiler.
endpoint specific	*
profilers)	
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	R-NO
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 nitroso compounds have the potential to be reduced, and
	then hydroxylated to an <i>N</i> -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 $S_N 1$ mechanism (Enoch et al 2010).
NO	OH O-acetyltransferase (R = -COCH ₃ ) (or) OR
1. Nitroreducta	se phosphotransferase (R = -PO ₃ ²⁻ ) (or)
2. N-hydroxyla	tion sulfotransferase ( $\mathbf{R} = -\mathbf{SO}_3^-$ )
	l l
	DNA adduct Nitrenium ion
	Nu = biological nucleophile
Set of chemicals used for	N/A – all structural alerts in this profiler were developed from a
profile development	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	An extensive review of the literature was performed enabling the
for profile development	chemistry associated with covalent binding to DNA to be defined and
	encoded in this profiler.
Performance of the	N/A – all alerts in this profiler were developed from a review of the
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual
the profile (for each	toxicological datasets were not analysed during the development of the
endpoint for the	alerts within this profiler.
endpoint specific	
profilers)	
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	OH
domain	R-N
	Н
	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
011	of reacting with DNA via an $S_N$ mechanism (Enoch et al 2010).
HN_OH	O-acetyltransferase ( $R = -COCH_3$ ) (or) OR
	phosphotransferase (R = -PO ₃ ²⁻ ) (or)
	sulfotransferase (R = $-SO_3^-$ )
	$\longrightarrow$ HN $\langle \rangle$
	NT .
	NU NH NH+
	$HN \qquad HN \qquad HN \qquad H$
	DNA adduct Nitrenium ion
	Nu = biological nucleophile
Set of chemicals used for	N/A – all structural alerts in this profiler were developed from a
profile development	review of the electrophilic chemistry associated with covalent DNA
	the chemistry for andmints where covalent hinding to DNA is the
	molecular initiating event
Data/Knowledge used	An extensive review of the literature was performed enabling the
for profile development	chemistry associated with covalent binding to DNA to be defined and
	encoded in this profiler.
Performance of the	N/A – all alerts in this profiler were developed from a review of the
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual
the profile (for each	toxicological datasets were not analysed during the development of the
endpoint for the	alerts within this profiler.
endpoint specific	
profilers)	
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	R1 - N = N - R2
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 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).
CH3	
N	
N ⁻¹	$NH_2$ 1 N budrowylation $NH+$
azoredu	ictase
HN AZOICU	$\rightarrow$ HN $\rightarrow$ LN $\rightarrow$ HN
	Nu
	nu
	nitrenium ion
	•
	Nu
	HŅ
	HN
	DNA adduct
	Nu – biological nucleonbile
Sat of chamicals used for	N/A all structural alerts in this profiler were developed from a
profile development	review of the electrophilic chemistry associated with covalent DNA
prome development	binding rather than an analysis of toxicological data. The alerts define
	the chemistry for endpoints where covalent hinding to DNA is the
	molecular initiating event
Data/Knowledge used	An extensive review of the literature was performed enabling the
for profile development	chemistry associated with covalent binding to DNA to be defined and
promo acronopment	encoded in this profiler.
Performance of the	N/A – all alerts in this profiler were developed from a review of the
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual
the profile (for each	toxicological datasets were not analysed during the development of the
endpoint for the	alerts within this profiler.
endpoint specific	<b>r</b>
profilers)	
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	$R1 \xrightarrow{O} R2$ $R1 \xrightarrow{I} R2$ $R1 = carbon \text{ or hydrogen}$
	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).
$H_{3}C$ $N$ $H_{3}C$ $H_{3}C$ $H$ $H_{3}C$ $H$ $H_{3}C$ $H$	$\rightarrow H_3C \underset{\text{CH}_3}{\overset{\text{O}}{\longrightarrow}} OH + HN \underset{\text{CH}_3}{\overset{\text{NH}_2}{\longrightarrow}} OH$
OH-	1. N-hydroxylation 2. O-acetyltransferase
	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	Ester heterocyclic hydroxylamines
Type of profile	Structural alert
Description/applicability domain	O H
	$R1^{N}O^{R2}$
	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
Mechanism	Desterification to produce a reactive nitrenium ion capable of reacting with DNA via an $S_N$ 1 mechanism is the most likely mechanism. This is a mechanism analogous to that which occurs in for aromatic systems (Enoch et al 2010).
$H = O \qquad Nu$ $H = O \qquad NH+$ $NH+$ $DNA adducts$	
Sat of chamicals used for	N(A = all structural slorts in this profiler were developed from a.
Set of chemicals used for	N/A – an structural alerts in this promet were developed from a
prome development	hinding rather than an analysis of toxicological data. The alorts define
	the chemistry for endpoints where covalent hinding to DNA is the
	molecular initiating event
Data/Knowledge used	An extensive review of the literature was performed enabling the
for profile development	chemistry associated with covalent binding to DNA to be defined and
<b>r</b>	encoded in this profiler.
Performance of the	N/A – all alerts in this profiler were developed from a review of the
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual
the profile (for each	toxicological datasets were not analysed during the development of the
endpoint for the	alerts within this profiler.
endpoint specific	
profilers)	
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	$ \begin{array}{c} R & O \\ N-N \\ R \\ R \end{array} $
Mechanism	R = aryl carbon (ring system can be aromatic or heteroaromatic) An S _N 1 nitrosation mechanism involving the cleavage of the N-N=O
	bond has been suggested as a route to DNA binding (Enoch et al 2010).
	N = N N = N N = O N
Set of chemicals used for	N/A - all structural alerts in this profiler were developed from a
profile development	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	N/A - all alerts in this profiler were developed from a review of the
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual
the profile (for each	toxicological datasets were not analysed during the development of the
endpoint for the	alerts within this profiler.
endpoint specific	
promers)	$E_{\rm max} = 1 + 1 + (2010) C_{\rm m} + (1 - 1) C$
Keierences	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	R
domain	R-N
	R V
	$\mathbf{R} = $ aliphatic $\mathbf{C}$
	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 $S_N$ 1 mechanism (Enoch et
	al 2010).
	$CHR_2$ $/CR_2$
R-	$-N \xrightarrow{2} R - N^{+}$
K	
	R R
	iminium ion (electrophile)
Set of chemicals used for	N/A – all structural alerts in this profiler were developed from a
profile development	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	An extensive review of the literature was performed enabling the
for profile development	chemistry associated with covalent binding to DNA to be defined and
	encoded in this profiler.
Performance of the	N/A – all alerts in this profiler were developed from a review of the
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual
the profile (for each	toxicological datasets were not analysed during the development of the
endpoint for the	alerts within this profiler.
endpoint specific	
profilers)	
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	$\begin{array}{c} R \\ K \\ R \\ R \\ H \end{array} $
	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 $S_N 2$ mechanism involving P450 epoxidation followed by an ring opening reaction has been suggested to lead to DNA alkylation (Enoch et al 2010).
$ \begin{array}{c} S \\ \end{array} \begin{array}{c} P450 \text{ epoxidation} \\ O \\ \end{array} \begin{array}{c} S \\ O \\ \end{array} \end{array} \begin{array}{c} S \\ O \\ \end{array} \begin{array}{c} HO \\ S \\ Nu \end{array} \end{array} $	
	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 $S_N^2$ mechanism with biological nucleophiles such as DNA (Enoch et al 2010).
	$\longrightarrow \bigcirc \bigcirc$
	Nu historial mulaarkila
Set of chemicals used for	N/A = all structural alerts in this profiler were developed from a
profile development	review of the electrophilic chemistry associated with covalent DNA
prome de veropment	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	An extensive review of the literature was performed enabling the
for profile development	chemistry associated with covalent binding to DNA to be defined and
	encoded in this profiler.
Performance of the	N/A – all alerts in this profiler were developed from a review of the
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual
the profile (for each	toxicological datasets were not analysed during the development of the
endpoint for the	alerts within this profiler.
endpoint specific	
profilers)	
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	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$
	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 $S_N 2$ attack by biological nucleophiles (Enoch et al 2010).
	$\sim$ $Cl$ $\sim$ $S$ $\sim$ $Nu$ $\sim$ $Cl$ $\sim$ $S$ $\sim$ $Nu$
	electrophile: episuitonium ion Cl $Nu$ $Cl$ $Nu$ $Cl$ $Nu$ $DNA adducts$ $Nu = biological nucleophile$
Set of chemicals used for	N/A – all structural alerts in this profiler were developed from a
profile development	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	An extensive review of the literature was performed enabling the
for profile development	encoded in this profiler
Performance of the	N/A – all alerts in this profiler were developed from a review of the
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual
the profile (for each	toxicological datasets were not analysed during the development of the
endpoint for the	alerts within this profiler.
endpoint specific	r
profilers)	
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	$X \xrightarrow{H} H H$ $X \xrightarrow{H} X$ $R R$ $X = Cl, Br, I$ $R = hydrogen any carbon$
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 $S_N 2$ type ring opening reaction (Enoch et al 2010).
CI	$HS \xrightarrow{G} \xrightarrow{G} \xrightarrow{G} \xrightarrow{S^+}_{Cl} \xrightarrow{S^-}_{G} \xrightarrow{G} \xrightarrow{S^+}_{G}$
Set of chemicals used for	N/A = all structural alerts in this profiler were developed from a
profile development	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
<b>Description/applicability</b>	$R_H_0$ , 0
domain	C' N'
	R
	$\mathbf{R}$ = any carbon or hydrogen
Mechanism	It has been suggested that a possible mechanism of action is an $S_{\rm w}^2$
Witchamsm	alkylation with the loss of the NO ₂ group (Enoch et al 2010)
$H_{C} \sim N_{N} \sim N_{1} \sim N_{1} \sim N_{2}$	
ſ	
Nu	
	Nu = biological nucleophile
Set of chemicals used for	N/A – all structural alerts in this profiler were developed from a
profile development	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	An extensive review of the literature was performed enabling the
for profile development	chemistry associated with covalent binding to DNA to be defined and
	encoded in this profiler.
Performance of the	N/A - all alerts in this profiler were developed from a review of the
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual
the profile (for each	toxicological datasets were not analysed during the development of the
endpoint for the	alerts within this profiler.
endpoint specific	
profilers)	
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	Q, S
domain	R2
	K N O S
	R H R
	$\mathbf{B} = any carbon or hydrogen$
Mechanism	The most likely mechanism leading to adduct formation has been
Wittenamsm	suggested to be an $S_{v2}$ alkylation reaction (Enoch et al 2010)
0	suggested to be an $S_N 2$ and yithfor reaction (Enotinet al 2010).
	Ŭ
H	CH ₃ CH ₃ CH ₃
	$H_1 = H_1 = H_2 $
ĊĤ,	
Å ³	
Nu -	
	Nu = biological nucleophile
Set of chemicals used for	N/A – all structural alerts in this profiler were developed from a
profile development	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
Data/Warawala data waad	Molecular initiating event.
for profile development	An extensive review of the interature was performed enabling the
for prome development	encoded in this profiler
Performance of the	N/A – all alerts in this profiler were developed from a review of the
nrofile / or Analysis of	chemistry associated with covalent DNA hinding Individual
the profile (for each	toxicological datasets were not analysed during the development of the
endpoint for the	alerts within this profiler.
endpoint specific	P-0
profilers)	
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	$\begin{array}{c} R \\ R - C \\ H \\ H \end{array}$
	$\label{eq:R} \begin{array}{l} R = \mbox{hydrogen, any carbon except the following:} \\ R \neq \mbox{carbonyl (these chemicals fall under the $\alpha$-halocarbonyl alert) -CS,} \\ -CN (these chemicals fall under the mustards alert) \\ X = \mbox{halogen} \end{array}$
Mechanism	An $S_N^2$ mechanism has been proposed as the primary method of DNA alkylation (Enoch et al 2010).
	Nu Cl Nu
	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	N/A - all alerts in this profiler were developed from a review of the
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual
the profile (for each	toxicological datasets were not analysed during the development of the
endpoint for the	alerts within this profiler.
endpoint specific	
profilers)	
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

Individual profile/alert	
Name	Sulfonates
Type of profile	Structural alert
Description/applicability	R2
domain	$0 HC - R^2$
	Ö
	R1 = any carbon
	R2 = any carbon, hydrogen
Mechanism	An $S_N 2$ mechanism has been proposed as the primary method of DNA
	alkylation (Enoch et al 2010).
	Nu
	3
$H_3C-S-O$	$\longrightarrow$ H ₃ C-S-OH + Nu-CH ₃
0	Nu – hielegigel nucleonhile
Sat of chamicals used for	N/A all structural elects in this profiler were developed from a
nrofile development	review of the electrophilic chemistry associated with covalent DNA
prome development	binding rather than an analysis of toxicological data. The alerts define
	the chemistry for endpoints where covalent hinding to DNA is the
	molecular initiating event
Data/Knowledge used	An extensive review of the literature was performed enabling the
for profile development	chemistry associated with covalent binding to DNA to be defined and
	encoded in this profiler.
Performance of the	N/A – all alerts in this profiler were developed from a review of the
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual
the profile (for each	toxicological datasets were not analysed during the development of the
endpoint for the	alerts within this profiler.
endpoint specific	
profilers)	
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

Individual profile/alert	
Name	Sulfates
Type of profile	Structural alert
Description/applicability	R2
domain	$\dot{Q}$ HC-R2
	R1 Ö
	R1 = any carbon
	R2 = any carbon, hydrogen
Mechanism	An $S_N 2$ mechanism has been proposed as the primary method of DNA
	alkylation (Enoch et al 2010).
	Nu O
O-S-O	$\rightarrow$ O-S-OH + Nu-CH ₃
$H_3C$ $H_3C$	$H_3C$ $H_0$
5 -	Nu = biological nucleophile
Set of chemicals used for	N/A – all structural alerts in this profiler were developed from a
profile development	review of the electrophilic chemistry associated with covalent DNA
r · · · · · · · · ·	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	An extensive review of the literature was performed enabling the
for profile development	chemistry associated with covalent binding to DNA to be defined and
	encoded in this profiler.
Performance of the	N/A – all alerts in this profiler were developed from a review of the
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual
the profile (for each	toxicological datasets were not analysed during the development of the
endpoint for the	alerts within this profiler.
endpoint specific	
profilers)	
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	Q R2
domain	
	$R1^{\Gamma}OHR2$
	R1 = any carbon
	R2 = any carbon, hydrogen
Mechanism	An $S_N 2$ mechanism has been proposed as the primary method of DNA
	alkylation (Enoch et al 2010).
0	Nu O
	$H \longrightarrow D + Nu-CH_2$
$H_{2}C^{P}O^{CP}$	H ₂ C ^P OH
3	3
	Nu = biological nucleophile
Set of chemicals used for	N/A – all structural alerts in this profiler were developed from a
profile development	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	An extensive review of the literature was performed enabling the
for profile development	chemistry associated with covalent binding to DNA to be defined and
Parformance of the	N/A = all alerts in this profiler were developed from a review of the
nrofile / or Analysis of	chemistry associated with covalent DNA hinding Individual
the profile (for each	toxicological datasets were not analysed during the development of the
endpoint for the	alerts within this profiler
endpoint for the	acto wianii uno promor.
profilers)	
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

	Individual profile/alert	
Name	Lactones	
Type of profile	Structural alert	
Description/applicability	<u>_0</u>	
domain		
	-0	
Mechanism	A ring opening $S_N^2$ mechanism has been proposed as the primary	
	method of DNA alkylation (Enoch et al 2010).	
	× · ·	
Nu		
	Nu – hielogical nucleanhile	
Sat of abomicals used for	N/A all structural elected in this profiler were developed from a	
set of chemicals used for profile development	N/A – all structural alerts in this promet were developed from a review of the electrophilic chemistry associated with covalent DNA	
prome development	binding rather than an analysis of toxicological data. The alerts define	
	the chemistry for endpoints where covalent hinding to DNA is the	
	molecular initiating event.	
Data/Knowledge used	An extensive review of the literature was performed enabling the	
for profile development	chemistry associated with covalent binding to DNA to be defined and	
	encoded in this profiler.	
Performance of the	N/A – all alerts in this profiler were developed from a review of the	
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual	
the profile (for each	toxicological datasets were not analysed during the development of the	
endpoint for the	alerts within this profiler.	
endpoint specific		
profilers)		
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 $S_N 2$ mechanism has been proposed as the primary method of DNA alkylation (Enoch et al 2010).
$( \bigcirc S \\ ( ) \\ ( \bigcirc S \\ ( ) \\ ( \bigcirc S \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( ) \\ ( $	
Nu	
	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	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
endpoint specific profilers)	
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

	Individual profile/alert
Name	Nitrosos
Type of profile	Structural alert
Description/applicability	R1, O
domain	N-N
	K2
	R1 = alkyl carbon
	R2 = alkyl C, aryl, C=O, C#N, S=O
Mechanism	An $S_N^2$ mechanism has been proposed as the primary method of DNA
	alkylation (Enoch et al 2010).
H ₃ C	_0 U
N-	
	$M \longrightarrow Nu = N = 0 \qquad H_3C^2 \qquad N_1$
H ₃ C	СН
0	
alaataan	Nu
electropi	
	Nu = biological nucleophile
Set of chemicals used for	N/A – all structural alerts in this profiler were developed from a
profile development	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
Data/Knowladge used	An extensive review of the literature was performed apphling the
for profile development	All extensive review of the interature was performed enabling the chamistry associated with covalent binding to DNA to be defined and
for prome development	encoded in this profiler
Performance of the	N/A – all alerts in this profiler were developed from a review of the
nrofile / or Analysis of	chemistry associated with covalent DNA hinding Individual
the nrofile (for each	toxicological datasets were not analysed during the development of the
endpoint for the	alerts within this profiler.
endpoint specific	and a strain and brounder
profilers)	
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748

	Individual profile/alert	
Name	Epoxides	
Type of profile	Structural alert	
Description/applicability	0	
domain	$\bigwedge$	
	$\mathbf{R}$   $\mathbf{R}$	
	R R	
	$\mathbf{R} = $ any carbon, hydrogen	
Mechanism	A ring opening S _N 2 mechanism has been proposed as the primary	
	method of DNA alkylation (Enoch et al 2010).	
	Nu Nu	
Nu		
	Nu = biological nucleophile	
Set of chemicals used for	N/A – all structural alerts in this profiler were developed from a	
profile development	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	An extensive review of the literature was performed enabling the	
for profile development	chemistry associated with covalent binding to DNA to be defined and	
	encoded in this profiler.	
Performance of the	N/A – all alerts in this profiler were developed from a review of the	
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual	
the profile (for each	toxicological datasets were not analysed during the development of the	
endpoint for the	alerts within this profiler.	
endpoint specific		
profilers)		
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748	
Individual profile/alert		
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Name	Aziridines	
Type of profile	Structural alert	
Description/applicability	N	
domain		
	R = R	
	R R	
	R = any carbon, hydrogen	
Mechanism	A ring opening $S_N 2$ mechanism has been proposed as the primary	
	method of DNA alkylation (Enoch et al 2010).	
H		
	$( \bigwedge^{N} \longrightarrow )_{NH} $	
	Nu	
	Nu = biological nucleophile	
Set of chemicals used for	N/A - all structural alerts in this profiler were developed from a	
profile development	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	An extensive review of the literature was performed enabling the	
for profile development	chemistry associated with covalent binding to DNA to be defined and	
	encoded in this profiler.	
Performance of the	N/A – all alerts in this profiler were developed from a review of the	
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual	
the profile (for each	toxicological datasets were not analysed during the development of the	
endpoint for the	alerts within this profiler.	
endpoint specific		
promers)		
Keferences	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748	

Individual profile/alert		
Name	Sulfuranes	
Type of profile	Structural alert	
Description/applicability	S	
domain		
	$\mathbf{R}$   $\mathbf{R}$	
	R R	
	$\mathbf{R} = $ any carbon, hydrogen	
Mechanism	A ring opening S _N 2 mechanism has been proposed as the primary	
	method of DNA alkylation (Enoch et al 2010).	
S SH		
	Nu Nu	
Nu		
	Nu = biological nucleophile	
Set of chemicals used for	N/A - all structural alerts in this profiler were developed from a	
profile development	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	An extensive review of the literature was performed enabling the	
for profile development	chemistry associated with covalent binding to DNA to be defined and	
	encoded in this profiler.	
Performance of the	N/A – all alerts in this profiler were developed from a review of the	
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual	
the profile (for each	toxicological datasets were not analysed during the development of the	
endpoint for the	alerts within this profiler.	
endpoint specific		
profilers)		
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748	

Individual profile/alert		
Name	Halogenated polarised alkenes (S _N 2)	
Type of profile	Structural alert	
Description/applicability	R X	
domain		
	$\mathbf{R} = $ any carbon, hydrogen, halogen	
	X = F, Cl, Br, l	
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 aldenyde (binding via an $S_N^2$ mechanism) (Enoch et al	
	2010).	
	$\langle \rangle$ $\langle \rangle$ $\langle \rangle$ $\langle \rangle$	
	$\underset{Cl}{\longrightarrow} Cl  V \overset{\circ}{\longrightarrow} Nu  V \overset{\circ}{\longrightarrow} V$	
CI	CI	
	Nu	
	$N_{\rm H}$ = biological nucleophile	
Set of chemicals used for	N/A – all structural alerts in this profiler were developed from a	
nrofile development	review of the electrophilic chemistry associated with covalent DNA	
prome de veropment	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	An extensive review of the literature was performed enabling the	
for profile development	chemistry associated with covalent binding to DNA to be defined and	
	encoded in this profiler.	
Performance of the	N/A – all alerts in this profiler were developed from a review of the	
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual	
the profile (for each	toxicological datasets were not analysed during the development of the	
endpoint for the	alerts within this profiler.	
endpoint specific		
profilers)		
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748	

]	Individual profile/alert
Name	Phenoxy polarised alkenes (S _N 2)
Type of profile	Structural alert
Description/applicability domain	$\begin{array}{c} R \\ \searrow \\ H \\ H \\ H \end{array}$
	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 $S_N 2$ mechanism) (Enoch et al 2010).
	Nu
N	Ju = 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	N/A - all alerts in this profiler were developed from a review
Analysis of the profile (for each	of the chemistry associated with covalent DNA binding.
endpoint for the endpoint specific profilers)	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	O O	
domain		
	R1 N V	
	$O_{R2}$	
	$\mathbf{D}_{1}$ = aromatic	
	$R_1 = aromatic$ $R_2 = any carbon$	
Machanism	$An S_{2}$ mechanism has been suggested to be responsible for the	
Witchamsm	alkylation of DNA (Enoch et al 2010).	
0 -	0 0	
	$N^{Nu} + HC^{-}$	
	$\rightarrow$	
Nu		
	Nu = biological nucleophile	
Set of chemicals used for	N/A – all structural alerts in this profiler were developed from a	
profile development	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	
Data/Knowledge used	An extensive review of the literature was performed enabling the	
for profile development	chemistry associated with covalent binding to DNA to be defined and	
for prome development	encoded in this profiler	
Performance of the	N/A – all alerts in this profiler were developed from a review of the	
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual	
the profile (for each	toxicological datasets were not analysed during the development of the	
endpoint for the	alerts within this profiler.	
endpoint specific		
profilers)		
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748	

Individual profile/alert		
Name	Thioureas	
Type of profile	Structural alert	
<b>Description/applicability</b>	H H	
domain		
	S	
	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 $S_N 2$ type	
	mechanism (Enoch et al 2010).	
H H	P450 H H H	
	$\longrightarrow$ $N N M \longrightarrow N N M$	
$\Pi_3 C$ $\Pi_3$	$H_3C$ $H_3C$ $H_3C$ $T$	
Ŝ	S _\	
	0 / × 2	
	Nu	
	¥	
	Н	
	$H_3C$ $\swarrow$ $CH_3$	
	Ńu	
	Nu = biological nucleophile	
Set of chemicals used for	N/A – all structural alerts in this profiler were developed from a	
profile development	review of the electrophilic chemistry associated with covalent DNA	
F	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	An extensive review of the literature was performed enabling the	
for profile development	chemistry associated with covalent binding to DNA to be defined and	
	encoded in this profiler.	
Performance of the	N/A – all alerts in this profiler were developed from a review of the	
profile / or Analysis of	chemistry associated with covalent DNA binding. Individual	
the profile (for each	toxicological datasets were not analysed during the development of the	
endpoint for the	alerts within this profiler.	
endpoint specific		
profilers)		
References	Enoch et al (2010) Critical Reviews in Toxicology, 40, p728-748	