#### About section of a profiler

#### Name of the profiler

Protein 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 a protein 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 protein binding for direct acting electrophiles only – 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. This profiler contains structural alerts for direct acting electrophiles only – oxidation and/or metabolism are not accounted for (appropriate Toolbox simulators should be applied, if required).

### **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 a protein. The structural alerts were derived from knowledge of the molecular initiating event covalently binding to a protein. 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 proteins. 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 a protein. 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 protein binding. Critical Reviews in Toxicology, 41, p783-802

#### Summary description of <u>profiles/alerts</u> 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 a protein.

#### Similar to other profilers

A number of related endpoint specific profilers exist in the OECD QSAR Toolbox relating to

genotoxicity. The protein 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. This profiler contains structural alerts for direct acting electrophiles only – oxidation and/or metabolism are not accounted for (appropriate Toolbox simulators should be applied, if required).

### 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 *Protein binding by OECD* has been rewritten but without modifying the knowledge and/or the logic it is based on. Only small 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.

Further general modifications are associated with the new 2D editor which allows the structural boundaries to be coded more accurately according to the descriptions of the categories.

Examples for categories with possible discrepancies between TB 3.4 and TB 4.0: Acetates; Allyl acetates and related chemicals.

#### 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 halides	
Type of profile	Structural alert	
Description/applicability	Y	
domain		
	$R \longrightarrow X$	
	R = any carbon, nitrogen	
	X (leaving group) = halogen, azide	
	Y = oxygen, sulphur	
Mechanism	An acylation mechanism involving nucleophilic attack at the carbonyl	
	(or sulfinyl) has been suggested as being responsible for the activity of	
	these chemicals (Enoch et al 2010).	
Cl $Nu$ + HCl		
. Nı	l	
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 protein	
	binding rather than an analysis of toxicological data. The alerts define	
	the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802

Individual profile/alert	
Name	Acetates
Type of profile	Structural alert
<b>Description/applicability</b>	Y
domain	.R2
	$R1 X^{R2}$
	R1 = any carbon or hydrogen
	R2 = aromatic, heteroaromatic, heterocyclic, alkene, alkyne
	R1 and R2 can be part of a ring e.g. dihydro-courmarin.
	Y = oxygen or sulphur
	X = oxygen (acetates), sulphur (thioacetates), nitrogen (acetanilides)
Mechanism	An acylation mechanism has been suggested for chemicals of this type
	(Enoch et al 2010).
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	$\mathbb{I} \longrightarrow \mathbb{I}_{0'} \longrightarrow \mathbb{I}_{0}$
\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	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 protein
1	binding rather than an analysis of toxicological data. The alerts define
	the chemistry for endpoints where covalent binding to a protein 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 a protein to be defined
D 6 641	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	chemistry associated with covalent a protein binding. Individual toxicological datasets were not analysed during the development of the
endpoint for the	alerts within this profiler.
endpoint specific	diens within this proffici.
profilers)	
References	Enoch et al (2010) Critical Reviews in Toxicology, 41, p783-802
<u> </u>	, , , , , , , , , , , , , , , , , , ,

## Individual profile/alert

Name	Anhydrides
	Structural alert
Type of profile	
Description/applicability	$Y_{II}$
domain	$\begin{bmatrix} X & Y & Y & Y & Y & Y & Y & Y & Y & Y &$
	X = oxygen, sulphur
	Y = oxygen (carbonyl), sulphur (sulfinyl)
	R = any carbon or hydrogen
Mechanism	An acylation mechanism has been suggested for chemicals of this type
	(Enoch et al 2010).
Nu = biological nucleophile  Set of chemicals used for profile development  N/A – all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent protein binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to a protein is the	
Doto/Wnoveledge used	molecular initiating event.  An extensive review of the literature was performed enabling the
Data/Knowledge used for profile development	chemistry associated with covalent binding to a protein 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 a protein 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, 41, p783-802

Individual profile/alert	
Name	Azlactones
Type of profile	Structural alert
Description/applicability domain	X = X $X = X$
	Y = oxygen (carbonyl), sulphur (sulfinyl) X = oxygen, sulphur, nitrogen
Mechanism	An acylation mechanism has been suggested for chemicals of this type. Importantly, these chemicals are only active due to the ability of the unsaturated moiety to stabilise the leaving group anion (the

	equivalent γ-lactone-type structures are not protein reactive) (Enoch et
	al 2010).
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	
${\sf H}^{^+}$	
$N_{\text{Nu}}$ OH	
	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 protein
1	binding rather than an analysis of toxicological data. The alerts define
	the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802

Individual profile/alert	
Name	Sulphonyl halides
Type of profile	Structural alert
Description/applicability domain	$\begin{array}{c} O \\ R - \stackrel{  }{S} - X \\ \stackrel{  }{O} \end{array}$
	R = any carbon or hydrogen X = halogen, cyano
Mechanism	An acylation mechanism involving attack at the sulphur has been suggested for the protein binding potential of this class of chemicals (Enoch et al 2010).
$H_{3}C - \stackrel{\circ}{\underset{O}{ }} - \stackrel{\circ}{\underset{O}{ }} - Cl \longrightarrow H_{3}C - \stackrel{\circ}{\underset{O}{ }} - Nu + Cl^{-}$	
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 protein binding rather than an analysis of toxicological data. The alerts define

	the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802

	Individual profile/alert	
Name	Phosphonic acid halides	
Type of profile	Structural alert	
Description/applicability	R O   O   O   O   O   O   O   O   O   O	
domain		
	0-P-X	
	٥	
	R	
	R = any carbon	
Mechanism	An acylation mechanism has been suggested a being responsible for	
	the protein binding ability of this class of chemicals (Enoch et al	
	2010).	
H <sub>2</sub> C (	0 . H.C 0	
3 - \	3 \	
0	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	
	0	
$H_3C$	Nu H <sub>3</sub> C	
	Nu = biological nucleophile	
Set of chemicals used for		
profile development	review of the electrophilic chemistry associated with covalent protein	
prome development	binding rather than an analysis of toxicological data. The alerts define	
	the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802	

Individual profile/alert	
Name	Dialkyl carbamoylhalides
Type of profile	Structural alert

Description/applicability	$\circ$
Description/applicability domain	
domain	R ,
	N X
	l R
	N 1 1
	X = halogen
36 3	R = any carbon
Mechanism	An acylation mechanism has been suggested a being responsible for
	the protein binding ability of this class of chemicals (Enoch et al
	2010).
	0
\	R $Nu + Cl$
R	$R_{N_1} + C_1$
	N Nu Ci
Ŕ	Ŕ
	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 protein
	binding rather than an analysis of toxicological data. The alerts define
	the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802

Individual profile/alert	
Name	β-Lactones
Type of profile	Structural alert
<b>Description/applicability</b>	ر0
domain	
	L-o
Mechanism	An acylation mechanism involving a ring opening reaction has been
	suggested to be responsible for the protein binding ability of these
	chemicals (Enoch et al 2010).
Nu O H HO 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 protein

	binding rather than an analysis of toxicological data. The alerts define
	the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802

	Individual profile/alert
Name	Thio-lactones
Type of profile	Structural alert
Description/applicability	v <sub>0</sub>
domain	
	$\sqsubseteq_{\mathbf{S}}$
Mechanism	An acylation mechanism involving a ring opening reaction has been
	suggested to be responsible for the protein binding ability of these
	chemicals (Enoch et al 2010).
	Nu +
	$HS \longrightarrow O$
	L-S <sub>2</sub> ) 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 protein
	binding rather than an analysis of toxicological data. The alerts define
	the chemistry for endpoints where covalent binding to a protein is the
D / /77	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 a protein 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 a protein 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	P
profilers)	
References	Enoch et al (2010) Critical Reviews in Toxicology, 41, p783-802

Individual profile/alert	
Name	α-Lactams
Type of profile	Structural alert

D 1: 1: 1:4		
Description/applicability	//0	
domain		
	$igsqcup_{ m N}$	
24 1 .	A 1.1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	
Mechanism	An acylation mechanism involving a ring opening reaction has been	
	suggested to be responsible for the protein binding ability of these	
	chemicals (Enoch et al 2010).	
	Nu Co	
	$H_{2N}$	
	→ 11 <sub>2</sub> 1√	
	└─Ŋ ) 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 protein	
1	binding rather than an analysis of toxicological data. The alerts define	
	the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802	

Individual profile/alert	
Name	Cyclopropenones
Type of profile	Structural alert
Description/applicability	0
domain	
	R R
	R = any carbon or hydrogen
Mechanism	An acylation mechanism involving a ring opening reaction has been
	suggested to be responsible for the protein binding ability of these
	chemicals (Enoch et al 2010).
$N_{\text{Nu}}$ $N_{\text{U}}$	
	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 protein
	binding rather than an analysis of toxicological data. The alerts define
	the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802

	Individual profile/alert
Name	Thiocyanates
Type of profile	Structural alert
<b>Description/applicability</b>	R-S=C=NH
domain	R = any carbon
Mechanism	An acylation mechanism has been suggested to be responsible for the
	protein reactivity of these chemicals (Enoch et al 2010).
	NH- H <sup>+</sup> NH <sub>2</sub>
-s=c=N	$H \longrightarrow S = \stackrel{\text{NH-}}{\longrightarrow} -S = \stackrel{\text{NH}_2}{\longrightarrow} -S = \text{$
	Nu Nu
	1Vu 1Vu
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 protein
	binding rather than an analysis of toxicological data. The alerts define
	the chemistry for endpoints where covalent binding to a protein is the
Data/Knowledge used	molecular initiating event.  An extensive review of the literature was performed enabling the
for profile development	chemistry associated with covalent binding to a protein to be defined
for prome development	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 a protein 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, 41, p783-802

Individual profile/alert	
Name	Isocyanates
Type of profile	Structural alert
<b>Description/applicability</b>	R-N=C=O
domain	R = any carbon
Mechanism	An acylation mechanism has been suggested to be responsible for the
	protein reactivity of these chemicals (Enoch et al 2010).

Individual profile/alert	
Name	Isothiocyanates
Type of profile	Structural alert
Description/applicability	R-N=C=S
domain	R = any carbon
Mechanism	An acylation mechanism has been suggested to be responsible for the
	protein reactivity of these chemicals (Enoch et al 2010).
	$S^ H^+$ SH
-N=C=S	$S \longrightarrow -N = \langle S^{-} \xrightarrow{H^{+}} -N = \langle SH \\ Nu & Nu \rangle = \langle SH \\ Nu & SH \\$
<b>/</b>	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 protein
_	binding rather than an analysis of toxicological data. The alerts define
	the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802

	Individual profile/alert
Name	Dithiocarbonimidic acid esters
Type of profile	Structural alert
Description/applicability	S-R
domain	R-N=C'
	R-N=C $S-R$ $S-R$
	R = any carbon
Mechanism	An acylation mechanism has been suggested to be responsible for the
	protein reactivity of these chemicals (Enoch et al 2010).
_	S - N = C $S - N = N = N$ $Nu$ $Nu$
	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 protein
	binding rather than an analysis of toxicological data. The alerts define
	the chemistry for endpoints where covalent binding to a protein 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 a protein to be defined
Performance of the	and encoded in this profiler.
profile / or Analysis of	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent a protein 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	dions within this profiler.
profilers)	
References	Enoch et al (2010) Critical Reviews in Toxicology, 41, p783-802

Individual profile/alert	
Name	Carbodiimides
Type of profile	Structural alert
<b>Description/applicability</b>	Ŗ
domain	N N
	N C N N R
	R = any carbon
Mechanism	An acylation mechanism has been suggested to be responsible for the protein reactivity of these chemicals (Enoch et al 2010).

$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	
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 protein binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802

Individual profile/alert	
Name	Ketenes
Type of profile	Structural alert
Description/applicability	R
domain	\ C-C-O
	R
	R = any carbon or hydrogen
Mechanism	An acylation mechanism has been suggested to be responsible for the
	protein reactivity of these chemicals (Enoch et al 2010).
$ \begin{array}{c} R \\ C = C = O \end{array} $ $ \begin{array}{c} H^{+} \\ Nu \end{array} $ $ \begin{array}{c} R \\ R \end{array} $ $ \begin{array}{c} Nu \\ R \end{array} $ $ \begin{array}{c} Nu \\ R \end{array} $ $ \begin{array}{c} Nu \\ R \end{array} $	
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 protein
	binding rather than an analysis of toxicological data. The alerts define
	the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802

Individual profile/alert		
Name	Polarised alkene - aldehydes	
Type of profile	Structural alert	
Description/applicability	R R	
domain		
	$R \longrightarrow O$	
	H H R H	
	R = any carbon or hydrogen	
Mechanism	A Michael addition mechanism has been suggested to be responsible	
	for the protein reactivity of these chemicals (Enoch et al 2010).	
	· → H <sup>+</sup>	
	П	
	O $Nu $ $C $ $O $ $Nu $ $O$	
1	$\rightarrow$ $\sim$ $\sim$	
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 protein	
	binding rather than an analysis of toxicological data. The alerts define	
	the chemistry for endpoints where covalent binding to a protein 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 a protein to be defined	
Performance of the	and encoded in this profiler.	
profile / or Analysis of	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent a protein 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	diens within this promer.	
profilers)		
References	Enoch et al (2010) Critical Reviews in Toxicology, 41, p783-802	
	Enter of all (2010) Children Reviews in Tomeology, 11, prod 002	

Individual profile/alert	
Name	Polarised alkene - ketones
Type of profile	Structural alert
Description/applicability domain	R1 $R1$ $R1$ $R1$ $R1$ $R1$ $R1$ $R1$

	R2 = any carbon		
Mechanism	A Michael addition mechanism has been suggested to be responsible		
	for the protein reactivity of these chemicals (Enoch et al 2010).		
$\begin{array}{cccccccccccccccccccccccccccccccccccc$			
Nu	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 protein		
	binding rather than an analysis of toxicological data. The alerts define		
	the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802		

Individual profile/alert		
Name	Polarised alkene - esters	
Type of profile	Structural alert	
Description/applicability	R1 R1	
domain	$R1 \downarrow O H \downarrow O$	
	$H O_{R2} R1 O_{R2}$	
	KZ KZ	
	R1 = any carbon or hydrogen	
	R2 = any carbon	
Mechanism	A Michael addition mechanism has been suggested to be responsible	
	for the protein reactivity of these chemicals (Enoch et al 2010).	
→ H <sup>+</sup>		
$\begin{array}{cccccccccccccccccccccccccccccccccccc$		
ÓM	le OMe OMe	
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 protein	
prome do veropinom	binding rather than an analysis of toxicological data. The alerts define	
	the chemistry for endpoints where covalent binding to a protein is the	
	the enemistry for enapoints where covarent emains to a protein 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 a protein 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 a protein 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, 41, p783-802

Individual profile/alert	
Name	Polarised alkene - amides
Type of profile	Structural alert
Description/applicability domain	R $R$ $O$ $H$ $R$
Mechanism	A Michael addition mechanism has been suggested to be responsible for the protein reactivity of these chemicals (Enoch et al 2010).
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	
/ NH	$NH_2$ $NH_2$
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 protein binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein binding. Individual toxicological datasets were not analysed during the development of the
endpoint for the endpoint specific profilers)	alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 41, p783-802

Individual profile/alert	
Name	Polarised alkene - nitros
Type of profile	Structural alert

Description/applicability	R R	
domain	R H	
	NO <sub>2</sub> NO <sub>2</sub>	
	H R	
	R = any carbon or hydrogen	
Mechanism	A Michael addition mechanism has been suggested to be responsible	
	for the protein reactivity of these chemicals (Enoch et al 2010).	
	<b>&gt;&gt;</b> H <sup>+</sup>	
	Nu C Nu	
NC NC	$NO_2 \rightarrow NO_2 \rightarrow NO_2$	
	- 2	
1		
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 protein	
	binding rather than an analysis of toxicological data. The alerts define	
	the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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)	F 1 1 (2010) G 11 1	
References	Enoch et al (2010) Critical Reviews in Toxicology, 41, p783-802	

Individual profile/alert	
Name	Polarised alkene - cyanos
Type of profile	Structural alert
Description/applicability	Ŗ Ŗ
domain	R $CN$ $H$ $CN$
	H R
	R = any carbon or hydrogen
Mechanism	A Michael addition mechanism has been suggested to be responsible
	for the protein reactivity of these chemicals (Enoch et al 2010).
$CN \longrightarrow Nu \longrightarrow C$ $CN \longrightarrow Nu \longrightarrow CN$	
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 protein
	binding rather than an analysis of toxicological data. The alerts define
	the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802

Individual profile/alert		
Name	Polarised alkene - sulfonates	
Type of profile	Structural alert	
Description/applicability	Ŗ1 Ŗ1	
domain	$\mathbf{p}_1 \downarrow 0 \qquad \mathbf{h} \downarrow 0$	
	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	
	R2 R2	
	R1 = any carbon or hydrogen	
	R1 = any  carbon of nydrogen R2 = any  carbon	
Mechanism	A Michael addition mechanism has been suggested to be responsible	
- Nacertainism	for the protein reactivity of these chemicals (Enoch et al 2010).	
	H	
0,0	$\mathbf{N} = \mathbf{C}^{-1} \mathbf{O} \qquad \mathbf{N} \mathbf{U} \qquad \mathbf{O}$	
S'	$\rightarrow$ Nu $\subset$ $S$	
	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	
	0	
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 protein	
	binding rather than an analysis of toxicological data. The alerts define	
	the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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)	F 1 (2010) G 11 1	
References	Enoch et al (2010) Critical Reviews in Toxicology, 41, p783-802	

	T 14 4 7 7 047 / 7 .
	Individual profile/alert
Name	Polarised alkene - sulfones
Type of profile	Structural alert
Description/applicability	Ŗ1 Ŗ1
domain	$\begin{bmatrix} & & & & & & & & & & & & & & & & & & &$
	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$
	$\frac{1}{\sqrt{2}} \frac{1}{\sqrt{2}} R2$ $\frac{1}{\sqrt{2}} \frac{1}{\sqrt{2}} R2$
	H O RI O
	R1 = any carbon or hydrogen
	R2 = any carbon
Mechanism	A Michael addition mechanism has been suggested to be responsible
	for the protein reactivity of these chemicals (Enoch et al 2010).
<u> </u>	Н
	$\begin{array}{cccccccccccccccccccccccccccccccccccc$
S'	$\rightarrow$ $\sim$
/ // `(	$CH_3 \qquad Nu \qquad C \qquad Nu \qquad Nu \qquad Nu \qquad Nu \qquad Nu \qquad Nu $
	0 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 protein
prome development	binding rather than an analysis of toxicological data. The alerts define
	the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802

Individual profile/alert	
Name	Polarised alkene - sulfinyls
Type of profile	Structural alert
<b>Description/applicability</b>	Ŗ1 Ŗ1
domain	R1 S O H S O H R2 R1 R2 R1 = any carbon or hydrogen R2 = any carbon
Mechanism	A Michael addition mechanism has been suggested to be responsible
	for the protein reactivity of these chemicals (Enoch et al 2010).

Individual profile/alert		
Name	Polarised alkene - oximes	
Type of profile	Structural alert	
Description/applicability	Ŗ Ŗ	
domain	H OH R OH	
7.5	R = any carbon or hydrogen	
Mechanism	A Michael addition mechanism has been suggested to be responsible for the protein reactivity of these chemicals (Enoch et al 2010).	
$N_{\text{Nu}}$ OH $N_{\text{Nu}}$ OH $N_{\text{Nu}}$ OH		
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 protein binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802

	Individual profile/alert
Name	Polarised alkene - pyridines
Type of profile	Structural alert
<b>Description/applicability</b>	R R R
domain	R N R N H N R N R
	R = any carbon or hydrogen
Mechanism	A Michael addition mechanism has been suggested to be responsible for the protein reactivity of these chemicals (Enoch et al 2010).
Nu $Nu$ $Nu$ $Nu$ $Nu$ $Nu$ $Nu$ $Nu$	
	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 protein
	binding rather than an analysis of toxicological data. The alerts define
	the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802

Individual profile/alert	
Name	Polarised alkene - pyrazines
Type of profile	Structural alert
<b>Description/applicability</b>	Ŗ Ŗ
domain	R N H N

	R = any carbon or hydrogen
Mechanism	A Michael addition mechanism has been suggested to be responsible
	for the protein reactivity of these chemicals (Enoch et al 2010).
Nu	$\begin{array}{cccccccccccccccccccccccccccccccccccc$
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 protein
	binding rather than an analysis of toxicological data. The alerts define
	the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802

	T 10 0 1 1 00 / 1 /
	Individual profile/alert
Name	Polarised alkene - pyrimidines
Type of profile	Structural alert
Description/applicability	R R R R
domain	R N R N H N R N R N
	$\begin{array}{cccccccccccccccccccccccccccccccccccc$
	R = any carbon or hydrogen
Mechanism	A Michael addition mechanism has been suggested to be responsible for
	the protein reactivity of these chemicals (Enoch et al 2010).
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	
	Nu = biological nucleophile
Set of chemicals used for	N/A – all structural alerts in this profiler were developed from a review
profile development	of the electrophilic chemistry associated with covalent protein binding

	rather than an analysis of toxicological data. The alerts define the
	chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802

	Individual profile/alert	
Name	Polarised alkene – triazines	
Type of profile	Structural alert	
Description/applicability domain	R R R N N 1,3,5-triazines	
	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	
	R R R 1,2,4-triazines	
	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	
	R = any carbon or hydrogen	
Mechanism	A Michael addition mechanism has been suggested to be responsible for	
	the protein reactivity of these chemicals (Enoch et al 2010).	
	${}^{\hspace{-2pt} \bullet} \operatorname{H}^{^{\hspace{-2pt} +}}$	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		
Nu		
	Nu = biological nucleophile	
Set of chemicals used for	N/A – all structural alerts in this profiler were developed from a review	
profile development	of the electrophilic chemistry associated with covalent protein binding	
	rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein binding. Individual	

the profile (for each endpoint for the endpoint specific profilers)	toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 41, p783-802

	Individual profile/alert	
Name	Azocarbonamides	
Type of profile	Structural alert	
Description/applicability	0	
domain	N. ND	
	$R N N N^{N}_2$	
	K <sub>2</sub> 1	
	0	
	R = any carbon or hydrogen	
Mechanism	A Michael addition mechanism has been suggested to be responsible	
	for the protein reactivity of these chemicals (Enoch et al 2010).	
0	0 0	
	N NH NH	
N' NH <sub>2</sub>	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	
H <sub>2</sub> N N		
( O	Nu OH Nu OH	
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 protein	
_	binding rather than an analysis of toxicological data. The alerts define	
	the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802	

Individual profile/alert	
Name	Polarised alkyne - aldehydes
Type of profile	Structural alert
<b>Description/applicability</b>	,O
domain	R————————————————————————————————————
	R = any carbon or hydrogen
Mechanism	A Michael addition mechanism has been suggested to be responsible

	,
	for the protein reactivity of these chemicals (Enoch et al 2010).
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	
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 protein
prome development	binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802

T 1° ° 1 1 0°1 / 1 /	
Individual profile/alert	
Name	Polarised alkyne - ketones
Type of profile	Structural alert
Description/applicability	$^{\prime}$ O
domain	R1———
	\
	R2
	R1 = any carbon or hydrogen
	R2 = any carbon
Mechanism	A Michael addition mechanism has been suggested to be responsible
	for the protein reactivity of these chemicals (Enoch et al 2010).
$\begin{array}{c} & & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & \\ & & & \\ &$	
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 protein
•	binding rather than an analysis of toxicological data. The alerts define
	the chemistry for endpoints where covalent binding to a protein 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 a protein to be defined
	and encoded in this profiler.
	1

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 a protein 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, 41, p783-802

Individual profile/alert	
Name Polarised alkyne - esters	
Type of profile	Structural alert
Description/applicability	
domain	0
domain	R1────────────────────────────────────
	O-R2
	R1 = any carbon or hydrogen
	R2 = any carbon
Mechanism	A Michael addition mechanism has been suggested to be responsible
	for the protein reactivity of these chemicals (Enoch et al 2010).
	+
	<b>→</b> H
	$O = N_{\rm H} \sim O$
	$O \longrightarrow Nu \longrightarrow C \longrightarrow Nu \longrightarrow O$
	OM.
ON	Me OMe OME
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 protein
	binding rather than an analysis of toxicological data. The alerts define
	the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802

Individual profile/alert	
Name	Polarised alkyne - amides
Type of profile	Structural alert
<b>Description/applicability</b>	,0
domain	R— <u>—</u> —∜
	N_D
	N-R
	R

	R = any carbon or hydrogen
Mechanism	A Michael addition mechanism has been suggested to be responsible
	for the protein reactivity of these chemicals (Enoch et al 2010).
	+
	<b>→</b> H
	- N O
	$0 \longrightarrow Nu / C / 0 \longrightarrow Nu / 0$
1	
l / 'nH	$N_{\rm H_2}$ $N_{\rm H_2}$
	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 protein
	binding rather than an analysis of toxicological data. The alerts define
	the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802
	1 = 10 th (= 010) elineal ite (10 %) in 10 meology, (1), p/05 002

T 10 0 1 1 G01 / 1 /	
	Individual profile/alert
Name	Polarised alkyne - nitros
Type of profile	Structural alert
Description/applicability	$R - NO_2$
domain	R = any carbon or hydrogen
Mechanism	A Michael addition mechanism has been suggested to be responsible for the protein reactivity of these chemicals (Enoch et al 2010).
$NU_{1}$ $NU_{2}$	
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 protein
	binding rather than an analysis of toxicological data. The alerts define
	the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein binding. Individual
<u> </u>	1 00 00 0000

the profile (for each endpoint for the endpoint specific profilers)	toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 41, p783-802

Individual moffle/cloud		
NT	Individual profile/alert	
Name	Polarised alkyne - cyanos	
Type of profile	Structural alert	
Description/applicability	R———CN	
domain	R = any carbon or hydrogen	
Mechanism	A Michael addition mechanism has been suggested to be responsible	
	for the protein reactivity of these chemicals (Enoch et al 2010).	
$CN \longrightarrow Nu \longrightarrow C$ $CN \longrightarrow Nu \longrightarrow CN$		
Nu		
114	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 protein	
Process and the process	binding rather than an analysis of toxicological data. The alerts define	
	the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802	

Individual profile/alert	
Name	Polarised alkyne - sulfonates
Type of profile	Structural alert
Description/applicability domain	R1 - = -S - O $C = R2$ $R1 - E = R2$
	R1 = any carbon or hydrogen R2 = any carbon
Mechanism	A Michael addition mechanism has been suggested to be responsible for the protein reactivity of these chemicals (Enoch et al 2010).

T 10 01 / 1 /		
N7	Individual profile/alert	
Name	Polarised alkyne - sulfones	
Type of profile	Structural alert	
Description/applicability domain	R1 - = -S - R2 O	
	R1 = any carbon or hydrogen	
	R2 = any carbon	
Mechanism	A Michael addition mechanism has been suggested to be responsible	
	for the protein reactivity of these chemicals (Enoch et al 2010).	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$		
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 protein	
prome development	binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802

Individual profile/alert		
Name	Polarised alkyne - sulfinyls	
Type of profile	Structural alert	
Description/applicability	.0	
domain	R1 - = S'	
	K1 — 5	
	R2	
	R1 = any carbon or hydrogen	
	R2 = any carbon	
Mechanism	A Michael addition mechanism has been suggested to be responsible	
	for the protein reactivity of these chemicals (Enoch et al 2010).	
	H	
$\int_{\infty}^{\infty} d\Omega$ Nu $\int_{\infty}^{\infty} d\Omega$ Nu $\int_{\infty}^{\infty} d\Omega$		
Ş	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	
/ CH	CH CH	
	$\operatorname{CH}_3$	
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 protein	
	binding rather than an analysis of toxicological data. The alerts define	
	the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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)	From the start (2010) Critical Provinces in Translates 41 702 002	
References	Enoch et al (2010) Critical Reviews in Toxicology, 41, p783-802	

Individual profile/alert	
Name	Polarised alkyne - pyridines
Type of profile	Structural alert
<b>Description/applicability</b>	$N = \setminus$
domain	$R \longrightarrow N$
	R = any carbon or hydrogen
Mechanism	A Michael addition mechanism has been suggested to be responsible
	for the protein reactivity of these chemicals (Enoch et al 2010).

Individual profile/alert	
Name	Polarised alkyne - pyrazines
Type of profile	Structural alert
Description/applicability domain	R-
	R = any carbon or hydrogen
Mechanism	A Michael addition mechanism has been suggested to be responsible for the protein reactivity of these chemicals (Enoch et al 2010).
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	
	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 protein binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to a protein 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 a protein to be defined and encoded in this profiler.
Performance of the profile / or Analysis of	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent a protein binding. Individual

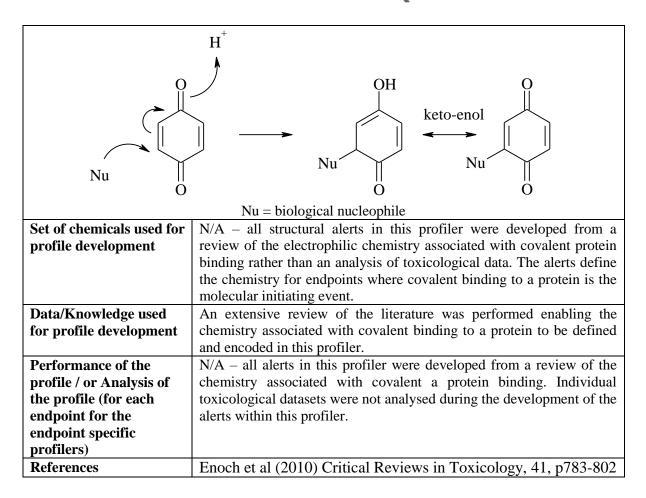
the profile (for each endpoint for the endpoint specific profilers)	toxicological datasets were not analysed during the development of the alerts within this profiler.
References	Enoch et al (2010) Critical Reviews in Toxicology, 41, p783-802

Individual profile/alert	
Name	Polarised alkyne - pyrimidines
Type of profile	Structural alert
Description/applicability domain	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$
	R = any carbon or hydrogen
Mechanism	A Michael addition mechanism has been suggested to be responsible for the protein reactivity of these chemicals (Enoch et al 2010).
$H^{^{+}}$	
N N	$\begin{array}{cccccccccccccccccccccccccccccccccccc$
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 protein
	binding rather than an analysis of toxicological data. The alerts define
	the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802

Individual profile/alert	
Name	Polarised alkyne - triazines
Type of profile	Structural alert

Description/applicability domain	$R - \frac{N}{N} $ 1,3,5-triazines	
	R = N = N $N = N $ $N = N$	
	R = N = N $N = N$ $N = N$ $N = 1,2,3-triazines$	
	R = any carbon or hydrogen	
Mechanism	A Michael addition mechanism has been suggested to be responsible for the protein reactivity of these chemicals (Enoch et al 2010).	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		
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 protein	
	binding rather than an analysis of toxicological data. The alerts define	
	the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802	

Individual profile/alert	
Name	Benzoquinones
Type of profile	Structural alert
Description/applicability domain	$\begin{array}{c} \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\$
Mechanism	A Michael addition mechanism has been suggested to be responsible for the protein reactivity of these chemicals (Enoch et al 2010).



Individual profile/alert	
Name	Quinone-methides
Type of profile	Structural alert
Description/applicability domain	H O H
Mechanism	A Michael addition mechanism has been suggested to be responsible for the protein reactivity of these chemicals (Enoch et al 2010).

OH 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 protein	
	binding rather than an analysis of toxicological data. The alerts define	
	the chemistry for endpoints where covalent binding to a protein 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 a protein to be defined	
Tot promo de Copino	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 a protein 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, 41, p783-802	

Individual profile/alert		
Name	Quinone-imines	
Type of profile	Structural alert	
Description/applicability domain	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	
Mechanism	A Michael addition mechanism has been suggested to be responsible for the protein reactivity of these chemicals (Enoch et al 2010).	
H <sup>+</sup> OH keto-enol Nu NH NH NH		

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 protein	
	binding rather than an analysis of toxicological data. The alerts define	
	the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802	

Individual profile/alert		
Name	Quinone-diimines	
Type of profile	Structural alert	
Description/applicability domain	N N N	
	H H	
Mechanism	A Michael addition mechanism has been suggested to be responsible for the protein reactivity of these chemicals (Enoch et al 2010).	
Nu = biological nucleophile  Set of chemicals used for profile development  N/A - all structural alerts in this profiler were developed from a review of the electrophilic chemistry associated with covalent protein binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to a protein 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 a protein to be defined and encoded in this profiler.	
Performance of the profile / or Analysis of the profile (for each and point for the	N/A – all alerts in this profiler were developed from a review of the chemistry associated with covalent a protein binding. Individual toxicological datasets were not analysed during the development of the alerts within this profiler.	
endpoint for the	aicus wiumi uns promei.	

endpoint specific profilers)	
References	Enoch et al (2010) Critical Reviews in Toxicology, 41, p783-802

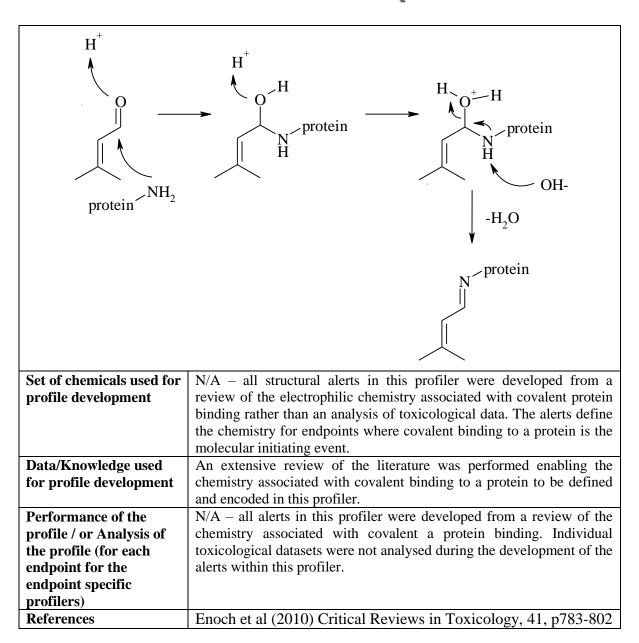
	Individual profile/alert
Name	Pyranones (and related nitrogen chemicals)
Type of profile	Structural alert
Description/applicability domain	$\begin{array}{cccccccccccccccccccccccccccccccccccc$
	Y = O, N
Mechanism	A Michael addition mechanism has been suggested to be responsible for the protein reactivity of these chemicals (Enoch et al 2010).
I	$\operatorname{I}^+$
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	
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 protein binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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)	E 1 (1/2010) C 2 1D 1 1
References	Enoch et al (2010) Critical Reviews in Toxicology, 41, p783-802

Individual profile/alert	
Name	Acid imides
Type of profile	Structural alert

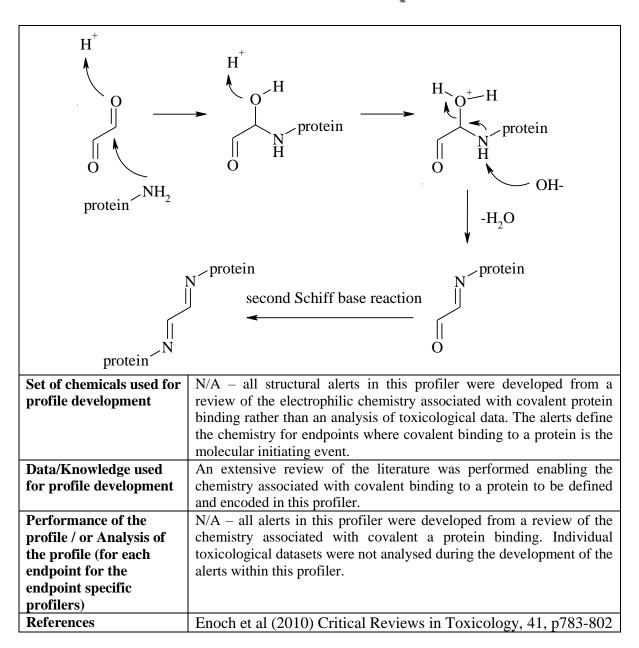
Description/applicability	0
domain	н, //
	$\bigvee$ N-R
	R
	O
	R = any carbon or hydrogen
Mechanism	A Michael addition mechanism has been suggested to be responsible
	for the protein reactivity of these chemicals (Enoch et al 2010).
	$\mathbf{H}^{^{+}}$
	П,
0	ОН О
	]
N-CH	$H_3 \longrightarrow N-CH_3 \longleftarrow N-CH_3$
	Nu Nu Nu
O O	Ö
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 protein
	binding rather than an analysis of toxicological data. The alerts define
	the chemistry for endpoints where covalent binding to a protein 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 a protein to be defined
for prome development	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 a protein 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, 41, p783-802

Individual profile/alert	
Name	Mono-carbonyls
Type of profile	Structural alert
Description/applicability domain	R $H$
	R = hydrogen, any carbon (R groups cannot be aromatic, heteroaromatic or heterocyclic, unless they are either mono- or diortho-substituted, R cannot be carbonyl as these chemicals fall under a separate structural alert)
Mechanism	A Schiff base mechanism has been suggested to be responsible for the protein reactivity of these chemicals (Enoch et al 2010).

Individual profile/alert	
Name	Di-substituted α,β-unsaturated aldehydes
Type of profile	Structural alert
Description/applicability domain	$ \begin{array}{c cccc} R & O & & R & R & O \\ \hline \downarrow & & & \downarrow & & \downarrow & \end{array} $
	R H R H  R = alkyl or aromatic carbon (including carbons in heterocyclic rings)
Mechanism	A Schiff base mechanism has been suggested to be responsible for the
Wiccianism	protein reactivity of these chemicals (Enoch et al 2010).



Individual profile/alert	
Name	1,2-Dicarbonyls
Type of profile	Structural alert
Description/applicability	Ö
domain	
	R K
	R = hydrogen, any carbon (both R groups cannot be aromatic,
	heteroaromatic or heterocyclic, unless they are either mono- or di-
	ortho-substituted)
Mechanism	A Schiff base mechanism has been suggested to be responsible for the
	protein reactivity of these chemicals (Enoch et al 2010).



Individual profile/alert	
Name	1,3-Dicarbonyls
Type of profile	Structural alert
<b>Description/applicability</b>	O O
domain	
	$R \nearrow R$
	R = hydrogen, any carbon (both R groups cannot be aromatic,
	heteroaromatic or heterocyclic, unless they are either mono- or di-
	ortho-substituted)
Mechanism	A Schiff base mechanism has been suggested to be responsible for the
	protein reactivity of these chemicals (Enoch et al 2010).

Individual profile/alert	
Name	Alkyl halides
Type of profile	Structural alert
Description/applicability	R
domain	R-C-X H
	$R = \mbox{hydrogen}$ , 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) $X = \mbox{Cl}$ , $F$ , $F$
Mechanism	An $S_N$ 2 mechanism has been suggested to be responsible for the protein reactivity of these chemicals (Enoch et al 2010).
$H_{3}C - X \xrightarrow{H^{+}} H_{3}C - R + HX$ Nu = biological nucleophile	
Set of chemicals used for	

profile development	review of the electrophilic chemistry associated with covalent protein binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802

Individual profile/alert	
Name	Sulfates
Type of profile	Structural alert
Description/applicability	
domain	D1 CIL O
	R1—CH O O—S—O O—R2
	O-S-O
	$\stackrel{\text{II}}{\text{O}}$ $\stackrel{\text{`R2}}{\text{R2}}$
	D1 one carbon budge con
	R1 = any carbon, hydrogen
	R2 = any carbon
Mechanism	Note: R1 and R2 can be part of an aliphatic ring system  An S <sub>N</sub> 2 mechanism has been suggested to be responsible for the
wiechamsm	protein reactivity of these chemicals (Enoch et al 2010).
Nu	protein reactivity of these elicinicals (Elioch et al 2010).
Nu	
<b>√</b>	
, ,	
$H_3C$	$\operatorname{H}^{^{ op}}$
(o-s-	$O \longrightarrow Nu-CH_3 + HO-S-O$
<b>—</b>	$O \longrightarrow Nu - CH_3 + HO - S - O \\ CH_3 \longrightarrow O CH_3$
C-4 -6 -1 1 1	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 protein binding rather than an analysis of toxicological data. The alerts define
	the chemistry for endpoints where covalent binding to a protein 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 a protein to be defined
202 Prome de l'écopment	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 a protein 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, 41, p783-802

Individual profile/alert	
Name	Sulfonates
Type of profile	Structural alert
Description/applicability	R1
domain	$p_1$ — $C_{\mu}$ 0
	R1 - CH
	$\overset{\sqcap}{O}$
	R1 = any carbon, hydrogen
	R1 = any carbon, flydrogen R2 = any carbon (R1 cannot be alkene or alkyne as these chemicals
	are Michael acceptors)
	Note: R1 and R2 can be part of an aliphatic ring system e.g. sultones
Mechanism	An $S_N^2$ mechanism has been suggested to be responsible for the
Witchamsin	protein reactivity of these chemicals (Enoch et al 2010).
Nu	<u> </u>
/ 110	
<b>√</b>	
H,C O	, , , , , , , , , , , , , , , , , , ,
3( 0-8)	—CH → Nu—CH + HO—S—CH
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	
O	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 protein
	binding rather than an analysis of toxicological data. The alerts define
	the chemistry for endpoints where covalent binding to a protein 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 a protein to be defined
D 6 64	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 a protein 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 Daviave in Taylorlagy, 41, 5792, 902
References	Enoch et al (2010) Critical Reviews in Toxicology, 41, p783-802

Individual profile/alert	
Name	Allyl acetates and related chemicals
Type of profile	Structural alert
<b>Description/applicability</b>	X
domain	$oxed{\hspace{0.1cm}}_{oxed{V}}$
	$R1 \xrightarrow{X} R2$
	X = oxygen, sulphur
	$Y = CH_2, CH$
	R1 = any carbon atom
	R2 = carbon atom part of an alkene, alkyne, aromatic ring,
	heteroaromatic ring or heterocyclic ring
Mechanism	An S <sub>N</sub> 2 mechanism has been suggested to be responsible for the
	protein reactivity of these chemicals (Enoch et al 2010).

	Individual profile/alert	
Name	Nitrosoureas (carbon)	
Type of profile	Structural alert	
Description/applicability	X	
domain	R1 NO	
	N N NO	
	R1 HC-R2	
	R2	
	X = oxygen (nitrosourea derivatives), nitrogen (nitrosoguanidine	
	derivatives)	
	R1 = any carbon, hydrogen	
	R2 = any carbon, hydrogen	
Mechanism	An S <sub>N</sub> 2 mechanism has been suggested to be responsible for the	
	protein reactivity of these chemicals (Enoch et al 2010).	
Ö	Q	
. N	$H^{\dagger}$ N. $\downarrow$	
O N	$NH_2 \xrightarrow{H^+} HO^{N} \xrightarrow{N} NH_2 + Nu-CH_3$	
	2	
CH <sub>3</sub>		
/		
Nu		
INU		
	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 protein	
	binding rather than an analysis of toxicological data. The alerts define	

	the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802

	Individual profile/alert	
Name	α-Halocarbonyls	
Type of profile	Structural alert	
Description/applicability	Y	
domain		
	$\mathbb{R}^{\mathbb{R}}$	
	X	
	Y = oxygen, sulphur	
	X = halogen	
	R = any carbon, hydrogen	
Mechanism	An S <sub>N</sub> 2 mechanism has been suggested to be responsible for the	
	protein reactivity of these chemicals (Enoch et al 2010).	
O Nu O		
Ĭ	$H_3C$ $CH_3$ $H_3C$ $CH_3 + Cl^-$	
u c	$CH_3$ $CH_3$ $CH_3$ $CH_3$ $CH_3$	
H <sub>3</sub> C	-   11 <sub>3</sub> C	
	Cl 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 protein	
	binding rather than an analysis of toxicological data. The alerts define	
	the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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)	Enoch et al (2010) Critical Deviana in Toxicalogy, 41, 2792, 902	
References	Enoch et al (2010) Critical Reviews in Toxicology, 41, p783-802	

Individual profile/alert	
Name	Phosphonates
Type of profile	Structural alert

Description/sliashilit-	<b>7.</b> 0	
Description/applicability	$R1 O \\ O-P-O \\ R HC-R2 \\ R2 \\ R1 = any carbon$	
domain	O-P-O	
	\   HC-D2	
	R nc k2	
	R2	
	R1 = any carbon	
	R2 = any carbon, hydrogen	
Mechanism	An S <sub>N</sub> 2 mechanism has been suggested to be responsible for the	
	protein reactivity of these chemicals (Enoch et al 2010).	
нс О	нс О	
O-P-	$O \rightarrow Nu-CH_3 + O-P-O$	
ĊH,	$CH_3$ $CH_2$	
3	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	
	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 protein	
r	binding rather than an analysis of toxicological data. The alerts define	
	the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802	

Individual profile/alert	
Name	Phosphates
Type of profile	Structural alert
Description/applicability domain	R1 O $O - P - O$ O $O - P - O$ $O - P - C$
	R2 = any carbon, hydrogen
Mechanism	An $S_N$ 2 mechanism has been suggested to be responsible for the protein reactivity of these chemicals (Enoch et al 2010).

	Individual profile/alert	
Name	Thiophosphates	
Type of profile	Structural alert	
Description/applicability	R1 S O-P-O HC-R2 R1 R2	
domain	0-P-0	
	\	
	R1 / C KZ	
	R1 R2	
	R1 = any carbon	
	R2 = any carbon, hydrogen	
Mechanism	An S <sub>N</sub> 2 mechanism has been suggested to be responsible for the	
	protein reactivity of these chemicals (Enoch et al 2010).	
$H_3C$ $S$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	
O-P-O	$O$ ) $\longrightarrow$ Nu-CH <sub>2</sub> + $O-P-O^-$	
	CH	
H.C	CH.	
1130	<b>\</b>	
	Nu	
	$H_3C$ $O$ $CH_3$ $O$ $O$ $CH_3$ $O$ $O$ $O$ $O$ $O$ $O$ $O$	
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 protein	
prome de cropment	binding rather than an analysis of toxicological data. The alerts define	
	the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802

	Individual profile/alert	
Name	α-Halo ethers	
Type of profile	Structural alert	
Description/applicability domain	C-O-C-X H	
	X = halogen	
36.1	R = any carbon atom, hydrogen	
Mechanism	An $S_N$ 2 mechanism has been suggested to be responsible for the protein reactivity of these chemicals (Enoch et al 2010).	
C-0-	$C-O-C-Cl \longrightarrow C-O-C-Nu + Cl$	
Nu	Nu	
1 14	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 protein	
prome de veropment	binding rather than an analysis of toxicological data. The alerts define	
	the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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)	E 1 (1/2010) C 22 1D 2 2 E 2 1 41 702 202	
References	Enoch et al (2010) Critical Reviews in Toxicology, 41, p783-802	

Individual profile/alert	
Name	β-Halo ethers
Type of profile	Structural alert
Description/applicability	Ŗ
domain	
	$C-O-CR_2-C-X$
	- H
	X = halogen
	R = any carbon atom, hydrogen
Mechanism	An S <sub>N</sub> 2 mechanism has been suggested to be responsible for the

	protein reactivity of these chemicals (Enoch et al 2010).	
$C-O-C-C-Cl \longrightarrow C-O-C-C-Nu + Cl$		
Nı	l 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 protein binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802	

	Individual profile/alert	
Name	Alkyl diazos	
Type of profile	Structural alert	
Description/applicability	R	
domain	HC-N=N-R	
	HC-N=N-R	
	R	
	X = halogen	
	R = any carbon atom, hydrogen	
Mechanism	An S <sub>N</sub> 2 mechanism has been suggested to be responsible for the	
	protein reactivity of these chemicals (Enoch et al 2010).	
$H_3C^{\prime}N=N-R$ $\longrightarrow$ $H_3C-Nu + N_2 + RH$		
<b>\</b>		
)		
N <sub></sub>		
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 protein	
	binding rather than an analysis of toxicological data. The alerts define	
	the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802

	Individual profile/alert	
Name	α-Haloalkenes (and related cyano, sulfate and sulphonate substituted	
Name	chemicals)	
Type of profile	Structural alert	
Description/applicability	R R	
domain		
domain	$R \nearrow R$	
	Ĭ Ť	
	k X	
	X = halogen, cyano, sulfate, sulphonate	
	R = any carbon, hydrogen	
Mechanism	An S <sub>N</sub> 2 mechanism has been suggested to be responsible for the	
112011011011	protein reactivity of these chemicals (Enoch et al 2010).	
Nu	1.	
	1144	
	$CH_3 \rightarrow CI^-$	
	Cl Nu	
7	Nu – higherical pugleophile	
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 protein	
prome development	binding rather than an analysis of toxicological data. The alerts define	
	the chemistry for endpoints where covalent binding to a protein 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 a protein to be defined	
F	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 a protein 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, 41, p783-802	

Individual profile/alert	
Name	α-Haloalkynes (and related cyano, sulfate and sulphonate substituted
	chemicals)
Type of profile	Structural alert
<b>Description/applicability</b>	R_
domain	R
	X

	X = halogen, cyano, sulfate, sulphonate
	R = any carbon, hydrogen
Mechanism	An S <sub>N</sub> 2 mechanism has been suggested to be responsible for the
	protein reactivity of these chemicals (Enoch et al 2010).
Nu	
$CH_3$ $CH_3$ $+$ $Cl^ Nu$ = 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 protein
prome de copment	binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802

	Individual profile/alert	
Name	α-Halobenzyls (and related cyano, sulfate and sulphonate substituted	
	chemicals)	
Type of profile	Structural alert	
Description/applicability	R1 R2	
domain	Y	
	X	
	X = halogen, cyano, sulfate, sulphonate	
	R1 = aromatic carbon	
	R2 = any carbon, hydrogen	
Mechanism	An S <sub>N</sub> 2 mechanism has been suggested to be responsible for the	
	protein reactivity of these chemicals (Enoch et al 2010).	
Nu	Nu	
$CH_3$ $CH_3$ $+$ $Cl^-$		
	Cl 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 protein	
	binding rather than an analysis of toxicological data. The alerts define	
	the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802

	Individual profile/alert	
Name	Epoxides	
Type of profile	Structural alert	
<b>Description/applicability</b>	Q	
domain		
	$R \cap R$ $R \cap R$	
	R = any carbon, hydrogen	
Mechanism	An S <sub>N</sub> 2 mechanism has been suggested to be responsible for the	
	protein reactivity of these chemicals (Enoch et al 2010).	
$O \longrightarrow H^+$ Nu $OH$		
	/ Nu	
IN IN	iu	
	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 protein	
	binding rather than an analysis of toxicological data. The alerts define	
	the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802	

Individual profile/alert	
Name	Aziridines
Type of profile	Structural alert

Description/applicability	Н	
domain	N N	
domani		
	$R \longrightarrow R$	
	$\begin{pmatrix} R & I & K \\ R & R \end{pmatrix}$	
	R = any carbon, hydrogen	
Mechanism	An $S_N$ 2 mechanism has been suggested to be responsible for the	
Witchamsm	protein reactivity of these chemicals (Enoch et al 2010).	
	N $N$ $N$ $N$ $N$ $N$ $N$ $N$ $N$ $N$	
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 protein	
	binding rather than an analysis of toxicological data. The alerts define	
	the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802	

Individual profile/alert	
Name	Sulfuranes
Type of profile	Structural alert
Description/applicability domain	$R \stackrel{S}{\underset{R}{\longrightarrow}} R$
	R = any carbon, hydrogen
Mechanism	An $S_N$ 2 mechanism has been suggested to be responsible for the protein reactivity of these chemicals (Enoch et al 2010).
S H <sup>+</sup> Nu SH	
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 protein
	binding rather than an analysis of toxicological data. The alerts define

	the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802

	Individual profile/alert	
Name	β-Lactones	
Type of profile	Structural alert	
Description/applicability domain	0	
Mechanism	An $S_N$ 2 mechanism has been suggested to be responsible for the protein reactivity of these chemicals (Enoch et al 2010).	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		
	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 protein binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802	

Individual profile/alert	
Name	Nitrosoureas (nitrogen)
Type of profile	Structural alert

Description/applicability	0
domain	Ĭ
domain	NO
	N N
	Ŕ
	R = any carbon, hydrogen
Mechanism	An S <sub>N</sub> 2 mechanism has been suggested to be responsible for the
	protein reactivity of these chemicals (Enoch et al 2010).
Nu _	
	0
\ \	$\ddot{\parallel}$ $_{\mathrm{H}^{+}}$ $\ddot{\parallel}$
N N	H H Nu-NO
$O \stackrel{\text{N}}{\stackrel{\text{N}}{\longrightarrow}} NH_2 \stackrel{\text{H}^+}{\longrightarrow} HN \stackrel{\text{N}}{\longrightarrow} NH_2 + Nu-NO$ $CH_3 \qquad CH_2$	
ĊH <sub>3</sub> ĊH <sub>3</sub>	
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 protein
_	binding rather than an analysis of toxicological data. The alerts define
	the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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 Deviews in Toyloglegy, 41, 2792, 902
Keterences	Enoch et al (2010) Critical Reviews in Toxicology, 41, p783-802

Individual profile/alert	
Name	Nitrosoguanidines (nitrogen)
Type of profile	Structural alert
Description/applicability	Ņ
domain	N NO N R
	R = any carbon, hydrogen
Mechanism	An $S_N$ 2 mechanism has been suggested to be responsible for the protein reactivity of these chemicals (Enoch et al 2010).
Nu NH	
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 protein binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to a protein is the molecular initiating event.
Data/Knowledge used	An extensive review of the literature was performed enabling the
8	
for profile development	chemistry associated with covalent binding to a protein 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 a protein 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, 41, p783-802

T. 1 1 C1 - /-1 4	
Individual profile/alert	
Name	N-Acetoxy-N-acetyl-phenyl
Type of profile	Structural alert
Description/applicability	$\mathbf{O}$
domain	
	R2 O
	) N
	$R_1 \stackrel{N}{\smile} K_2$
	0
	R1 = aromatic, heteroaromatic, heterocyclic ring system
	R2 = any carbon, hydrogen
Mechanism	An S <sub>N</sub> 2 mechanism has been suggested to be responsible for the
	protein reactivity of these chemicals (Enoch et al 2010).
O	•
l i	
	+ Nu O
H <sub>3</sub> C O	H I II
N CH <sub>2</sub> N CH <sub>3</sub> +	
	$H_3C$ OH
1 1 1	
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 protein
_	binding rather than an analysis of toxicological data. The alerts define
	the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802

Individual profile/alert	
Name	N-Acyloxy-N-alkoxyamides
Type of profile	Structural alert
Description/applicability domain	R1 $N$ $O$ $R2$ $O$ $R2$
Mechanism	$R1 = aromatic$ , heteroaromatic, heterocyclic ring system $R2 = any \ carbon$ , hydrogen $R1 = aromatic$ An $S_N2$ mechanism has been suggested to be responsible for the
171CHamsiii	protein reactivity of these chemicals (Enoch et al 2010).
Nu Nu H <sub>3</sub> C O CH <sub>3</sub>	
	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 protein binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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)	F 1 - 1/2010) G 12 1 D 1 - 1 T 1 1 1 1 1 702 002
References	Enoch et al (2010) Critical Reviews in Toxicology, 41, p783-802

Individual profile/alert	
Name	Isothiazol-3-ones (sulphur)
Type of profile	Structural alert
Description/applicability	Ö
domain	
	$R \sim R$
	\\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\
	<u> </u>
	R
	R = any carbon, hydrogen, halogen

Mechanism	An S <sub>N</sub> 2 mechanism has been suggested to be responsible for the
	protein reactivity of these chemicals (Enoch et al 2010).
ON CH <sub>3</sub> H <sup>+</sup> protein S N CH <sub>3</sub>	
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 protein
_	binding rather than an analysis of toxicological data. The alerts define
	the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802

Individual profile/alert	
Name	Isothiazolin-3-ones (sulphur)
Type of profile	Structural alert
Description/applicability domain	O
	$R \longrightarrow N - R$ $R$
	R = any carbon, hydrogen, halogen
Mechanism	An $S_N$ 2 mechanism has been suggested to be responsible for the protein reactivity of these chemicals (Enoch et al 2010).
ON CH <sub>3</sub> H <sup>+</sup> protein S N CH <sub>3</sub>	
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 protein binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802

	Individual profile/alert
Name	Aromatic sulphonic acids
Type of profile	Structural alert
Description/applicability domain	O 
	R <sup>S</sup> OH
	R = aromatic, heteroaromatic, heterocyclic ring system
Mechanism	An $S_N$ 2 mechanism has been suggested to be responsible for the protein reactivity of these chemicals (Enoch et al 2010).
O S O O	$\begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} C \\ S \\ O\end{array} \end{array}$
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 protein binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein binding. Individual
the profile (for each endpoint for the	toxicological datasets were not analysed during the development of the alerts within this profiler.
endpoint specific	alerts within this proffici.
profilers)	
References	Enoch et al (2010) Critical Reviews in Toxicology, 41, p783-802

Individual profile/alert	
Name	Thiocyanates
Type of profile	Structural alert
<b>Description/applicability</b>	R
domain	`s−c≡n
	R = any carbon
Mechanism	An S <sub>N</sub> 2 mechanism has been suggested to be responsible for the

	protein reactivity of these chemicals (Enoch et al 2010).
H <sub>3</sub> C	H <sub>3</sub> C
, S	$H_3C$ $S-S$ $+$ HCN protein
(	protein
protein	
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 protein binding rather than an analysis of toxicological data. The alerts define
	the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802

	Individual profile/alert
Name	Thiols
Type of profile	Structural alert
<b>Description/applicability</b>	R—SH
domain	R = any carbon
Mechanism	An $S_N$ 2 mechanism has been suggested to be responsible for the protein reactivity of these chemicals (Enoch et al 2010).
	H <sub>3</sub> C protein
	$S-H$ $\longrightarrow$ $S-S$
	$H_3C$
SH	
protein	<del>-</del>
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 protein
	binding rather than an analysis of toxicological data. The alerts define
	the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802

	Individual profile/alert
Name	Disulfides
Type of profile	Structural alert
<b>Description/applicability</b>	R-S-S-R
domain	R = any carbon
Mechanism	An $S_N$ 2 mechanism has been suggested to be responsible for the protein reactivity of these chemicals (Enoch et al 2010).
H <sub>3</sub> C S	$CH_3$ $\rightarrow$ $S-S$ protein $+$ $H_3C-SH$
SH	
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 protein binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802

	Individual profile/alert	
Name	Thiosulfonates	
Type of profile	Structural alert	
<b>Description/applicability</b>	,O	
domain	R-S-S	
	R	
	R = any carbon	
Mechanism	An S <sub>N</sub> 2 mechanism has been suggested to be responsible for the	
	protein reactivity of these chemicals (Enoch et al 2010).	
H <sub>3</sub> C <sub>\</sub>		
$H_3C$ $H_3C$ $S-S$ $S-S$ $H_3C$ $H_$		
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 protein binding rather than an analysis of toxicological data. The alerts define	

	the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802

	Individual profile/alert
Name	Sulfoxides of disulfides
Type of profile	Structural alert
Description/applicability domain	$ \begin{array}{c} O \\   \\ R - S - S = O \\   \\ R \\ R = \text{any carbon} \end{array} $
Mechanism	An $S_N$ 2 mechanism has been suggested to be responsible for the protein reactivity of these chemicals (Enoch et al 2010).
H <sub>3</sub> C S-	$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$
protein	
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 protein binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802

Individual profile/alert	
Name	Sulfenyl halides
Type of profile	Structural alert
<b>Description/applicability</b>	R-S-X
domain	X = halide

	R = any carbon, hydrogen
Mechanism	An S <sub>N</sub> 2 mechanism has been suggested to be responsible for the
	protein reactivity of these chemicals (Enoch et al 2010).
$H_3C-S$	$H_3C-S-S$ -protein + HCl
1	
SH	
protein	
Set of chemicals used for	N/A – all structural alerts in this profiler were developed from a
	review of the electrophilic chemistry associated with covalent protein
profile development	•
	binding rather than an analysis of toxicological data. The alerts define
	the chemistry for endpoints where covalent binding to a protein is the
D / ///	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 a protein 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 a protein 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, 41, p783-802

Individual profile/alert	
Name	N-Chloro-sulphonamides
Type of profile	Structural alert
Description/applicability	0
domain	$R - \stackrel{  }{S} - \stackrel{H}{N}$
	O Cl
	R = any carbon, hydrogen
Mechanism	An $S_N$ 2 mechanism has been suggested to be responsible for the protein reactivity of these chemicals (Enoch et al 2010).
H <sub>3</sub> C $-$ S $-$ N $)$ H <sub>3</sub> C $-$ S $-$ NH <sub>2</sub> + protein Cl	
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 protein binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802

Individual profile/alert	
Name	<i>N</i> -Haloimides
Type of profile	Structural alert
Description/applicability domain	
	R N R I X
	R = any carbon, hydrogen $X = F$ , Cl, Br, I
Mechanism	An $S_N$ 2 mechanism has been suggested to be responsible for the protein reactivity of these chemicals (Enoch et al 2010).
	$CH_{a} \longrightarrow H_{a}C \longrightarrow N \longrightarrow CH_{a} + protein \longrightarrow Cl$
H <sub>3</sub> C N	$CH_3$ $H_3C$ $N$ $CH_3$ + protein $N$ $Cl$
Ci	
NH <sub>2</sub>	
protein	
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 protein
	binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802

Individual profile/alert	
Name	Polarised alkenes with a halogen leaving group
Type of profile	Structural alert

Description/applicability	X
domain	
	Н
	X = F, Cl, Br, I
Mechanism	An S <sub>N</sub> 2 mechanism has been suggested to be responsible for the
	protein reactivity of these chemicals (Enoch et al 2010).
protein	· •
	NH <sub>2</sub>
	protein—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 protein
	binding rather than an analysis of toxicological data. The alerts define
	the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802

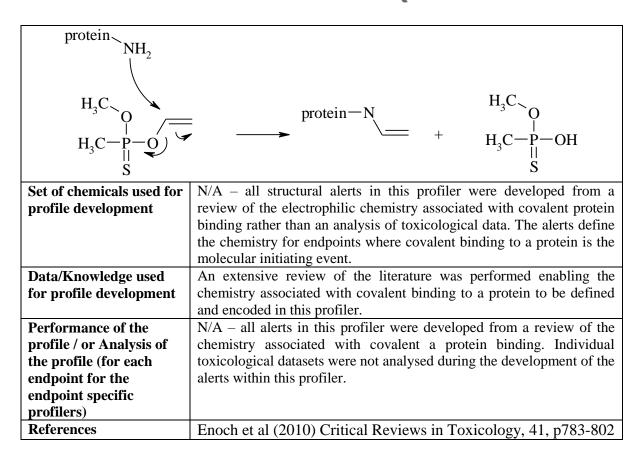
Individual profile/alert	
Name	Polarised alkenes with a sulfonate leaving group
Type of profile	Structural alert
Description/applicability domain	$ \begin{array}{c} O \\ -S \\ -R \\ -R \\ O \end{array} $
	R = any carbon
Mechanism	An $S_N$ 2 mechanism has been suggested to be responsible for the protein reactivity of these chemicals (Enoch et al 2010).
protein $NH_2$ $0$ $H_3C-S-O$ O	$= \longrightarrow \begin{array}{c} \text{protein-N} & O \\ + H_3C - S - OH \\ O \end{array}$
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 protein binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to a protein 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 a protein to be defined
for prome development	
	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 a protein 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, 41, p783-802

	Individual profile/alert	
Name	Polarised alkenes with a sulfate leaving group	
Type of profile	Structural alert	
Description/applicability domain	$O = \begin{cases} O \\   \\ O = \\ O \end{cases}$ $O = \begin{cases} O \\   \\ O = \\ O \end{cases}$ $O = \begin{cases} O \\   \\ O = \\ O = \\ O = \end{cases}$ $O = \begin{cases} O \\   \\ O = \end{cases}$ $O = \begin{cases} O \\   $	
Mechanism	An $S_N$ 2 mechanism has been suggested to be responsible for the protein reactivity of these chemicals (Enoch et al 2010).	
protein $NH_2$ $O-S-O$ $H_3C$ $O$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	
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 protein binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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)	E 1 (1/2010) C 2 1	
References	Enoch et al (2010) Critical Reviews in Toxicology, 41, p783-802	

Individual profile/alert	
Name	Polarised alkenes with a phosphonate leaving group
Type of profile	Structural alert
Description/applicability	O O
domain	
domani	$= \begin{pmatrix} I \\ O - P - O \\ R \\ R \end{pmatrix}$
	$\longrightarrow$ $\stackrel{\mid}{\longrightarrow}$ $\stackrel{\mid}{\triangleright}$ $\stackrel{\mid}{\triangleright}$
	\ R R
	H
	R = any carbon
Mechanism	An S <sub>N</sub> 2 mechanism has been suggested to be responsible for the
	protein reactivity of these chemicals (Enoch et al 2010).
protein	
$NH_2$	
\	
	и с
$H_3C$	nrotein—N
	protein—N 3 O
$H_3C$ $O$ $H_3C-P-O$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$
, II ~	
0	<u> </u>
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 protein
	binding rather than an analysis of toxicological data. The alerts define
	the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802

Individual profile/alert	
Name	Polarised alkenes with a thiophosphonate leaving group
Type of profile	Structural alert
Description/applicability domain	$O - P - O$ $= \begin{cases}                                   $
Mechanism	An $S_N$ 2 mechanism has been suggested to be responsible for the protein reactivity of these chemicals (Enoch et al 2010).



Individual profile/alert	
Name	Polarised alkenes with a phosphate leaving group
Type of profile	Structural alert
Description/applicability domain	$= \bigvee_{O-P-O}^{O} \bigcap_{R}^{R}$
	n
7.7	R = any carbon
Mechanism	An $S_N$ 2 mechanism has been suggested to be responsible for the protein reactivity of these chemicals (Enoch et al 2010).
	protein reactivity of these chemicals (Enoch et al 2010).
H <sub>3</sub> C O O O O O O O O O O O O O O O O O O O	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$
Set of chemicals used for profile development	review of the electrophilic chemistry associated with covalent protein binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802

	Individual profile/alert	
Name	Polarised alkenes with a thiophosphate leaving group	
Type of profile	Structural alert	
Description/applicability domain	$= \bigvee_{H}^{S} \bigwedge_{R}^{R}$	
	R = any carbon	
Mechanism	An $S_N$ 2 mechanism has been suggested to be responsible for the protein reactivity of these chemicals (Enoch et al 2010).	
protein $NH_2$ $H_3C$ $O$ $O$ $H_3C$ $S$ Set of chemicals used for	protein—N $+ \begin{array}{c} H_3C \\ O \\ O \\ H_3C \\ S \end{array}$ $N/A - \text{all structural alerts in this profiler were developed from a}$	
profile development	review of the electrophilic chemistry associated with covalent protein binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein binding. Individual toxicological datasets were not analysed during the development of the	
endpoint for the endpoint specific profilers)	alerts within this profiler.	
References	Enoch et al (2010) Critical Reviews in Toxicology, 41, p783-802	

Individual profile/alert	
Name	Mustards
Type of profile	Structural alert

Description/applicability	D D D II
Description/applicability domain	$\left[\begin{array}{cccc} R & R & H \\ I & I & I \end{array}\right]$
domain	$X \xrightarrow{K} Y \xrightarrow{K} X$
	$egin{array}{cccccccccccccccccccccccccccccccccccc$
	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
76.1	R = any carbon, hydrogen
Mechanism	An $S_N$ 2 mechanism has been suggested to be responsible for the
	protein reactivity of these chemicals (Enoch et al 2010).
	$\wedge$
S	$S \longrightarrow S$
CI, $\wedge$ CI	Cl' V Nu Cl' V Nu
	electrophile: episulfonium ion
	1 1
	$\wedge$
$\sim$	$\longrightarrow$ CI $\stackrel{\downarrow}{N_{\text{U}}}$ $\stackrel{\downarrow}{N_{\text{U}}}$ $\stackrel{\downarrow}{N_{\text{U}}}$ $\stackrel{\downarrow}{N_{\text{U}}}$
CI	Cl V Nu Cl V V Nu
	electrophile: aziridinium ion Protein 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 protein
	binding rather than an analysis of toxicological data. The alerts define
	the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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	E 1 (1/2010) C :: 1
Rafarancas	Enoch et al (2010) Critical Reviews in Toxicology, 41, p783-802

Individual profile/alert	
Name	1,2-Dihaloalkanes
Type of profile	Structural alert
Description/applicability domain	$X \xrightarrow{H} \xrightarrow{H} X$ $X = R$ $X = Cl, Br, I$ $R = \text{hydrogen, any carbon}$
Mechanism	An $S_N$ 2 mechanism has been suggested to be responsible for the protein reactivity of these chemicals (Enoch et al 2010).

Individual profile/alert	
Name	Activated halo-benzenes
Type of profile	Structural alert
Description/applicability domain	X Y
	X (leaving group) = F, Cl, Br, I, CN Y (activating group) = aldehyde, nitro, cyano, halogen, sulfinyl, sulfone, sulfonate, trifluoromethyl
Mechanism	A $S_N$ Ar mechanism has been suggested to be responsible for the protein reactivity of these chemicals (Enoch et al 2010).
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	
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 protein binding rather than an analysis of toxicological data. The alerts define
	<u> </u>

	the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802

	Individual profile/alert
Name	Activated halo-pyridines
Type of profile	Structural alert
Description/applicability	X X
domain	Y, Y, ,
	N/
	1N
	X (leaving group) = F, Cl, Br, I, CN
	Y (activating group) = aldehyde, nitro, cyano, halogen, sulfinyl,
1.	sulfone, sulfonate, trifluoromethyl
Mechanism	An S <sub>N</sub> Ar mechanism has been suggested to be responsible for the
	protein reactivity of these chemicals (Enoch et al 2010).
Nu Cl	C1 A Nu
	Nu CI
	N N
$\downarrow$	Y
NO.	$NO_2$ $NO_2$
	1.02
	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 protein
	binding rather than an analysis of toxicological data. The alerts define
	the chemistry for endpoints where covalent binding to a protein 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 a protein to be defined
<b>T</b>	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 a protein 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)	

	Individual profile/alert
Name	Halo-pyrimidines
Type of profile	Structural alert
Description/applicability	X X
domain	
	X (leaving group) = F, Cl, Br, I, CN
Mechanism	An $S_N$ Ar mechanism has been suggested to be responsible for the protein reactivity of these chemicals (Enoch et al 2010).
Nu Cl	Nu Cl
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 protein
	binding rather than an analysis of toxicological data. The alerts define the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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 Daviava in Taxicalage: 41, 2792, 202
References	Enoch et al (2010) Critical Reviews in Toxicology, 41, p783-802

Individual profile/alert	
Name	Halo-triazines
Type of profile	Structural alert
Description/applicability	X
domain	
	$N \nearrow N$
	N/
	IN .
	X (leaving group) = $F$ , $Cl$ , $Br$ , $I$ , $CN$
Mechanism	An S <sub>N</sub> Ar mechanism has been suggested to be responsible for the
	protein reactivity of these chemicals (Enoch et al 2010).

Nu Cl	Nu Cl
	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 protein
	binding rather than an analysis of toxicological data. The alerts define
	the chemistry for endpoints where covalent binding to a protein 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 a protein 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 a protein 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, 41, p783-802