

Appendix Table 1. The summary of immunotoxicological data of 25 chemicals

Immunotoxicity classification				NTP data				The data collected by the VMT															
Chemical name	Classification	Rationale	In vivo				Mode of action	In vitro effect on IL-2				In vitro effect on IFN-γ				In vitro effect on IL-4							
			Immune system organ weight	Cytokine production	TDA R	Cytokine production		T cell proliferation	Effect	Animal	In vitro (method)	References	Effect	Animal	In vitro (method)	References	Effect	Animal	In vitro (method)	References			
Phase I study																							
Dibutyl phthalate	TTIC	3), 4)	A (spleen)			S (IL-2, 4, IFN-γ)(H) A (IL-1β)(H) x 3 S (IL-1β)	This compound then is proposed to modulate cytokine secretion from both monocytes/macrophages and T cells.					S	human	T cells (in vitro)	Hansen et al. 2015	S	human	T cells (in vitro)	Hansen et al. 2015 (0.0275–27.8 ug/mL)				
Hydrocortisone	TTIC	1)	S (thymus) x 2 S (spleen)		N	S (IFN-α)		S	human	lymphocyte (in vitro)	Chikanda and Panayi 1993					S	mouse	splenocyte (ex vivo)	Fernandez-Cabazade et al. 2007	A	mouse	splenocyte (ex vivo)	Fernandez-Cabazade et al. 2007
								S	human	PBL (in vitro)	Goodwin et al. 1986					no effect	mouse	cell line (EL-4)	Wagner et al. 2006	A	mouse	cell line (EL-4)	Wagner et al. 2006
Lead(II) acetate	TTIC	1)	A (thymus)		S N	S (IFN-γ, IL-1β)(H) A (IL-4)(H)	S (H)					S	human	PBMC	Herndan et al. 2005		human	PBMC (in vitro)			rat	?	Chen et al. 2004
Nickel(II) sulfate	TTIC	1)	N S (thymus)		N	A (IL-4, IFN-γ)(H) S (IL-2) S (IFN-γ)		A (NIC2)	mouse	spleen cell (in vitro)	Kim et al. 2009	A (NIC2)	mouse	spleen cell (in vitro)	Kim et al. 2009	A	human	PBMC (in vitro)	Thomas et al. 2003				
dimethylthiocarbamate (DMDTC)	NTIC					S (IL-1β)	N (H)																
Phase II study																							
X																							
X																							
2,4-diaminotoluene	NTIC		N (spleen) A (spleen)		S	-	-																
Benzo(a)pyrene	TTIC	2), 3)		S (IL-2)	S x 5 A	A (IL-4)(H) N (IFN-γ)(H) N (IL-2)(H) S (IL-2, 4, IFN-γ)	S (H) x 2 S x 6	Disruption of T-cell activities has been associated with B[a]P induced immunotoxic effects (Ueno et al. 1986).															
Cadmium Chloride			A (spleen) S (spleen)	A (IL-2) N (IFN-γ)	S x 4	A (IFN-γ)(H) S (IL-2, IFN-γ) A (IFN-γ) S (IL-2) A (IL-2)	S		N (ex vivo), A (in vitro)	rat	splenocyte (ex vivo, in vitro)	Wang et al. 2017	no effect	rat	spleen cell (ex vivo)	Demersku et al. 2014							
		2), 3)							S (IC50=7.05E-05 M) S	mouse	PBMC (in vitro)	Kooljman et al. 2010											
Dibromosuccinic acid (DBAA)	TTIC	1), 4)	A (spleen) S (thymus) x 2		N	S (IL-2, 4)	S	Overall, studies suggest that DBAA produces immunotoxic effects through modulation of T-cell mediated cell immunity. T-cell apoptosis, through extrinsic and intrinsic pathways, are proposed to play a role in the mode of action.															
Diethylstilbestrol (DES)	TTIC	1), 2), 4)	S (thymus) x 4 A (thymus) x 2 A (spleen)	A (IFN-γ) x 3	S	A (IL-1) A (IL-2)		DES exposure was associated with down-regulation of gene expression in the TCR complex, and the TCR and CD28 signaling pathways.															
Diphanylhydantoin	TTIC	2), 3), 4)		A (IL-4) S (IFN-γ, IL-2) S (IL-1α) S (IL-4, 17)	S A x 2	-	-	DPH treatment can lead to a decrease of suppressor T cells															
Ethylene Dibromide (EDB)	TTIC	1)	S (thymus) S (spleen) N		A	-	S																
Glycidol	NTIC		N		S	-	-	omases suggest that glycidol measures a-cis function, and NK cell and macrophage															
Indomethacin	TTIC	3), 4)	N A (spleen)		S x 3 A x 1	A (IL-2)(H) A (IFN-γ)(H)	A (H) x 4 S A x 3	indomethacin inhibition of prostaglandin synthesis leads to altered T-cell function.															
Isonicotinic Acid Hydratide (IAH)	TTIC	2)	N x 2			S (IL-2)(H) A (IL-2)(H) S (IL-1)(H)	S (H) x 3 A (H) x 6 A N	effects on T-cell function may play a role in increased susceptibility to L. monocytogenes (Burns et al. 1994).	A	human	PBMC (in vitro), cell line (Jurkat)	Tsui et al. 1995											
Nitrobenzene	Undetermined		A (spleen) x 3 A (thymus) x 2 S (thymus) x 2 S (spleen) x 2 N		N	-																	
Urethane, Ethyl carbamate	TTIC	1)	A (thymus) A (spleen)	N (IL-2)	S x 2 N	N (IL-2, 4, IFN-γ)(H) A (IFN-γ)(H) S (IFN-γ)(H)	N x 2																
Tributyltin Chloride (TBTC)	TTIC	1)	S (thymus) x 4 S (spleen) x 3		N S	A (IFN-γ)(H) N (IL-2, 4)(H) S (IFN-γ)(H)	S (H) S x 3		no effect (TBTC)	mouse	cell line (EL-4)	Ringenke et al. 2005											
Perfluorooctanoic Acid (PFOA)	TTIC	1)	S (thymus) x 2 S (spleen) x 2	N (IFN-γ)		S (IL-4)(H) N (IL-2)(H)	A (H) S (H) N (H)	Direct modulation of NF-κB has been implicated in modulation of cytokine production and secretion (Cossini et al. 2012).															
Dichloroacetic Acid (DCAA)	TTIC	2), 3)		N (IL-2) A (spleen) x 3 S (IL-4) x 2 S (IL-2)	N	A (IL-2)(H) A (IL-2, IFN-γ)		T-cell activation was one proposed mode of action for DCAA.															
Toluene	NTIC		N		N		N																
Acetonitrile	NTIC		S (thymus)		S	-	-																
Mannitol	NTIC						N (H)																
Vanadium Pentoxide	NTIC		N A (spleen)			N	N																
o-Benzyl-p-chlorobenzal (BCP)	NTIC		N		N	-	-																

The criterion number used to define immunotoxicity

Appendix Table 2. The summary of immunotoxicological data of 60 chemicals in the IL-2

Chemical name	Immunotoxicity classification		Thymus weight		Ex Vivo effect on IL-2		In vitro effect on IL-2		In vitro effect on IFN-γ		In vitro effect on IL-4			
	Classification	Rationale ^a	Weight	Animal	Reference	Effect	Animal	In vitro (method)	Reference	Effect	Animal	In vitro (method)	Reference	
FK506	TTC	1,3	decrease	rat	Nelken et al. 1987		S	rat	cell line (EL-4)	Wagner et al. 2006	S	rat	cell line (EL-4)	Wagner et al. 2006
	TTC	1,3	decrease	rat	Tabi et al. 1990		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
Cyclosporine A	TTC	1,3	decrease	mouse	Audi et al. 2012		S	human	cell line (3A9 T cell hybridoma)	Yoshimura et al. 1989				
	TTC	1,3	decrease	mouse	Buchanan et al. 1987		S	mouse	cell line (EL-4)	Ringier et al. 2005	S	mouse	cell line (EL-4)	Ringier et al. 2005
Adriamycin D	TTC	3	no effect	mouse	Hattori et al. 1987		S	mouse	cell line (Junkat, Hu-7b)	Gabryel et al. 2004				
	TTC	2,3	decrease	mouse	Hattori et al. 1987		S	mouse	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
Digoxin	TTC	3	no effect	mouse	Karimov et al. 1989		S	human	cell line (3A9 T cell hybridoma)	Yoshimura et al. 1989				
	TTC	2,3	decrease	mouse	Buchanan et al. 1987		S	mouse	cell line (EL-4)	Ringier et al. 2005	S	mouse	cell line (EL-4)	Ringier et al. 2005
Colchicine	TTC	2,3	decrease	mouse	Hattori et al. 1987		S	mouse	cell line (Junkat, Hu-7b)	Gabryel et al. 2004				
	TTC	2,3	decrease	mouse	Hattori et al. 1987		S	mouse	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
FR157863	Undetermined	2,3	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
	Undetermined	1	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
Benzothiazolium chloride	Undetermined	1	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
	Undetermined	1	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
Mercuric chloride	TTC	1,3	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
	TTC	1,3	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
Chlorpromazine	Undetermined	1	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
	Undetermined	1	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
Amphetamine B	Undetermined	1	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
	Undetermined	1	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
Dibutyl phthalate	Undetermined	1	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
	Undetermined	1	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
2-Aminocaproic acid	Undetermined	1	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
	Undetermined	1	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
Formaldehyde	Undetermined	1	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
	Undetermined	1	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
Pyrimethamine	Undetermined	1	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
	Undetermined	1	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
Isopropyl alcohol	Undetermined	1	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
	Undetermined	1	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
Cisplatin	TTC	1,2,3	decrease	mouse	Kouchak et al. 1996		S	mouse	cell line (EL-4)	Wagner et al. 2006				
	TTC	1,2,3	decrease	mouse	Kouchak et al. 1996		S	mouse	cell line (EL-4)	Wagner et al. 2006				
Cobalt chloride	TTC	1,3	decrease	mouse	Chetty et al. 1979		S	mouse	cell line (EL-4)	Wagner et al. 2006				
	TTC	1,3	decrease	mouse	Chetty et al. 1979		S	mouse	cell line (EL-4)	Wagner et al. 2006				
Chloroquine	TTC	1,3	decrease	mouse	Chetty et al. 1979		S	mouse	cell line (EL-4)	Wagner et al. 2006				
	TTC	1,3	decrease	mouse	Chetty et al. 1979		S	mouse	cell line (EL-4)	Wagner et al. 2006				
Microcystin	Undetermined	1	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
	Undetermined	1	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
Mitomycin C	Undetermined	1	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
	Undetermined	1	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
Hydrogen peroxide	Undetermined	1	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
	Undetermined	1	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
Cital	Undetermined	1	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
	Undetermined	1	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
Dexamethasone	TTC	1,3	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
	TTC	1,3	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
Pentamidine isethionate	TTC	3	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
	TTC	3	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
Lead(II)acetate	TTC	1,3	increase	rat	Burn et al. 2001		S	mouse	cell line (EL-4)	Wagner et al. 2006				
	TTC	1,3	increase	rat	Burn et al. 2001		S	mouse	cell line (EL-4)	Wagner et al. 2006				
Azathioprine	TTC	1,2,3	decrease	mouse	Nakazaki et al. 1987		S	mouse	cell line (3A9 T cell hybridoma)	Yoshimura et al. 1989				
	TTC	1,2,3	decrease	mouse	Nakazaki et al. 1987		S	mouse	cell line (3A9 T cell hybridoma)	Yoshimura et al. 1989				
Diesel exhaust particle	TTC	1,3	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
	TTC	1,3	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
Sodium dodecyl sulfate	TTC	3	No Effect	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
	TTC	3	No Effect	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
Dapsone	NTIC	1	No Effect	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
	NTIC	1	No Effect	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
Nitrofurantoin	TTC	1,3	increase, decrease	mouse	Nakazaki et al. 1987		S	mouse	cell line (EL-4)	Wagner et al. 2006				
	TTC	1,3	increase, decrease	mouse	Nakazaki et al. 1987		S	mouse	cell line (EL-4)	Wagner et al. 2006				
p-Nitroaniline	TTC	1,3	increase, decrease	mouse	Nakazaki et al. 1987		S	mouse	cell line (EL-4)	Wagner et al. 2006				
	TTC	1,3	increase, decrease	mouse	Nakazaki et al. 1987		S	mouse	cell line (EL-4)	Wagner et al. 2006				
Sulfasalazine	TTC	1,3	increase, decrease	mouse	Nakazaki et al. 1987		S	mouse	cell line (EL-4)	Wagner et al. 2006				
	TTC	1,3	increase, decrease	mouse	Nakazaki et al. 1987		S	mouse	cell line (EL-4)	Wagner et al. 2006				
Aluminum chloride	TTC	1,3	increase, decrease	mouse	Nakazaki et al. 1987		S	mouse	cell line (EL-4)	Wagner et al. 2006				
	TTC	1,3	increase, decrease	mouse	Nakazaki et al. 1987		S	mouse	cell line (EL-4)	Wagner et al. 2006				
Nickel sulfate	TTC	1,3	increase, decrease	mouse	Nakazaki et al. 1987		S	mouse	cell line (EL-4)	Wagner et al. 2006				
	TTC	1,3	increase, decrease	mouse	Nakazaki et al. 1987		S	mouse	cell line (EL-4)	Wagner et al. 2006				
Hydrocortisone	Undetermined	1	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
	Undetermined	1	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
Dichloroamine	Undetermined	1	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
	Undetermined	1	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
Chloroplatinic acid	Undetermined	1	No Effect	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
	Undetermined	1	No Effect	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
Sodium bromate	NTIC	1	No Effect	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
	NTIC	1	No Effect	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
Histamine	TTC	3	No Effect	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
	TTC	3	No Effect	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
Isotriazolin	Undetermined	1	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
	Undetermined	1	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
Triethanolamine	Undetermined	1	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
	Undetermined	1	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
Magnesium sulfate	TTC	1,3	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
	TTC	1,3	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
Rapamycin	Undetermined	1	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
	Undetermined	1	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
Mazotiline	Undetermined	1	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
	Undetermined	1	decrease	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
Wafarin	TTC	3	No Effect	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
	TTC	3	No Effect	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
2,4-Diaminobenzene	NTIC	1	No Effect	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
	NTIC	1	No Effect	mouse	Nakazaki et al. 1987		S	human	cell line (Junkat, Hu-7b)	Henderson et al. 1991				
Cyclophosphamide														