Industrial Injuries Advisory Council - Information note

Lung cancer and dioxin

December 2013

1. During a recent horizon scanning exercise, the Industrial Injuries Advisory Council (IIAC) identified lung cancer and work involving exposure to dioxin as a potential topic for review. This stemmed from the Council's consideration of the Health and Safety Executive's (HSE) priorities for cancer (HSE Executive Board meeting paper HSE/12/36) and the results of the HSE's commissioned research project *Cancer Burden in the UK* by Rushton et al, 2010.

2. Dioxins are a group of chemical contaminants that persist in the environment and accumulate in the fatty tissues of animals. They are highly stable, and, once inside the body can be stored for many years. Dioxins are a group of structurally similar compounds, the most toxic of which is 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD); but the group also includes other dioxins and dioxin-related compounds including biphenyls (PCBs), dibenzofurans (PCDF) and polychlorinated dibenzodioxins (PCDDs). They are produced as by-products of a variety of industrial processes (e.g. chemical and pesticide manufacture), and combustion activities (e.g. waste incineration).

3. Occupational exposure to dioxins can occur in, amongst others, chemical workers producing herbicides, pesticide applicators and municipal waste incinerator workers. However, due to the ubiquitous nature of dioxins in the environment the majority of the general population will have had low level, background exposure to dioxins via the food chain. For example, in Seveso, Italy, in 1976, two kilograms of TCDD were released into the atmosphere as the result of an accidental explosion. Veterans of the Vietnam War were also exposed to TCDD via exposure to the herbicide, Agent Orange.

4. In 1997, the International Agency for Research on Cancer (IARC) classified dioxin as a group 1 (established) human carcinogen based on limited evidence of harm in humans but sufficient evidence in experimental animals, and extensive research indicating that TCDD acts through the aryl hydrocarbon receptor. This receptor is found in humans and animals and is involved in a number of key regulatory pathways. Disruption of these pathways may be associated with cancer development through changes in tumour suppressor proteins, growth factors, oncogenes and other cellular components essential for normal physiology and development.

5. Exposure to dioxin has been linked to small excesses in cancers in a multitude of sites, including the lung. The action of TCDD on the aryl hydrocarbon receptor in producing a carcinogenic effect at numerous

unrelated sites is unprecedented. IIAC conducted a search of the research literature and a preliminary analysis of key papers (see Table). The relative risk of cancers at all sites was generally between 1.1 and 1.5 (Manuwald et al, 2012; Ruder et al, 2011; McBride et al 2009; Crump et al, 2003, Bertazzi et al, 2001; Steenland et al, 1999 and 2001; Flesch-Janys et al, 1998; Michalek et al, 1998; Kogevinas et al, 1997; Becher et al, 1996; Ott and Zober, 1996; Zober et al, 1994; Fingerhut et al, 1991; Thiess et al, 1982), although some studies have not found any increased risk of cancer due to exposure to dioxin (Boers et al, 2012; Collins et al, 2009a and 2009b; 't Mannetje et al, 2005; Bodner et al 2003; Starr et al, 2001).

6. For lung cancer, six studies were noted in which no increased risk of lung cancer in dioxin-exposed workers was observed (Boers et al, 2012; Bodner et al, 2003; Collins et al 2009a and 2009b; McBride et al, 2009 and Mannes et al, 2005). There was also a large body of evidence (13 studies) showing an increased risk of lung cancer from dioxin exposure, although the relative risk was generally less than 1.4 (Manuwald et al, 2012; Ruder et al, 2011; Jones et al 2009; 't Mannetje et al, 2005; Bertazzi et al, 2001; Steenland et al, 1999; Michaelek et al, 1998; Mahan et al, 1997; Kogevinas et al, 1997; Becher et al, 1996; Collins et al, 1993; Coggon et al, 1991 and Fingerhut et al 1991). Certain of these studies identified too few workers with lung cancer in the cohort to be able to provide reliable statistical information about the risks specific to lung cancer. The risks specific to lung cancer appear to be no larger than the risks of any other of the cancers linked to occupational exposure to dioxin. Furthermore, the risks specific to lung cancer, or at any other sites, due to dioxin exposure are not more than doubled.

7. In considering whether to recommend to Minister that a condition and its exposure is eligible for prescription IIAC seek evidence that the risk of a particular disease is greater than doubled in exposed workers compared with a suitable comparator population. As indicated above, this threshold has not been reached for lung cancer and exposure to dioxin. IIAC has, therefore, concluded that this exposure-outcome circumstance does not warrant prescription. The Council will, however, keep the topic under review.

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Table: Evidence tables for lung cancer and dioxin exposure

Study	Work	Exposure	Country	Risks for lung cancer	Risks for all cancers
Boers et al 2012	Chlorophenoxy herbicides, chlorophenols and contaminants (n=187)	TCDD	Denmark	"No relationships found between TCDD exposure and mortality from…respiratory cancer".	HR for all cancers 1.08 (95% CI 1.03-1.13)
Manuwald et al 2012 (Mortality study)	Chemical plant (n=1,191 men)	Dioxin	"Hamberg cohort"	SMR for respiratory cancer 1.64 (95% CI 1.32-2.03)	SMR for all cancer 1.37 (95% CI 1.21-1.56
Ruder et al 2011 (Mortality study)	PCP production workers (n=2,122) and sub-group of TCDD workers (n=720)	PCP, TCDD	US	SMR 1.36 (95% CI 1.13-1.62) for trachea, bronchus and lung (for PCP workers)	(Unclear if this is risk for sub-group of TCDD exposed workers) Total cancers (SMR 1.17; 95% CI 1.05-1.31)
Collins et al 2009 (a) (Mortality study)	PCP manufacturers (n=773)	PCP	US	SMR "near expected levels" for lung cancer	SMR "near expected levels" for all cancers combined
McBride et al 2009 (Mortality study)	TCP manufacturers (n=1,599)	TCDD	New Zealand	SMR 0.8 (95% CI 0.4-1.5)	No trends with exposure levels. Total cancers (SMR 1.1; 95% CI 0.9-1.4)
Collins et al 2009 (b) (Mortality study)	TCP production (n=1,615)	TCDD	US	SMR 0.7 (95% CI 0.5-0.9)	Total cancers (SMR 1.0; 95% CI 0.8-1.1)

Jones et al 2009 (Mortality study meta-analysis)	Crop protection production industry	Mixed, included dioxin		Significantly raised for lung cancer	
Consonni et al 2008 (Mortality study)	Seveso inhabitants (n=278,108)	TCDD	Italy		No mention of lung cancer
Mannes et al 2005 (Mortality study)	Chemical manufacturing plant	Dioxin	New Zealand	Case incidence and mortality rate for lung cancer did not differ significantly	
't Mannetje et al 2005 (Mortality study)	Phenoxy herbicide producers (n=813) and sprayers (n=699)	Dioxins	New Zealand	Trachea, bronchus and lung cancer SMR for producers 1.37 (95% CI 0.71-2.39) SMR for sprayers 0.45 (95% CI 0.18-1.09)	SMR for producers 1.24 (95% CI 0.90-1.67) SMR for sprayers 0.82 (95% CI 0.57-1.14)
Bodner et al 2003 (Mortality study)	Chemical production workers (n=2,187); of whom developed chloracne (n=245)	TCDD	US	SMR 0.8 (95% CI 0.6-1.1) SMR for chloracne sufferers 0.3 (95% CI 0-1.1)	All cancer SMR 1 (95% CI 0.8-1.1) All cancers SMR for chloracne sufferers i.e. highly exposed 0.5 (95% CI 0.3-1.0)
Crump et al 2003 (Meta-analysis)					Statistically significant relationship between all cancers and dioxin
Bertazzi et al 2001 (Mortality study)	Seveso inhabitants (n= 6,745) 20 year follow up	Dioxin	Italy	SMR 1.3 (95% CI 1.0-1.7); no latency related pattern	All cancer SMR 1.3 (95% CI 1.0-1.7)

Revich et al 2001 (Mortality study)	Crop protection chemical production plant (residents living 1-3 km away; non-occupational)	Dioxin	Chapaevsk, Russia	SMR 3.1 (95% CI 2.6-3.8)	
Starr et al 2001 (Meta analysis)					No statistically significant relationship between all cancer and dioxin
Steenland et al 1999, 2001 (Mortality study)	Industrial cohorts ("NIOSH cohort" used by IARC for group 1 classification) (n=5,132 at 12 plants)	TCDD	"NIOSH cohort"; US	"Statistically significant"	All cancer SMR 260 ppt yr 0.98 402 0.90 853 1.14 1,895 1.18 4,420 1.33 12,125 1.69 59,838 1.54
Flesch-Janys et al 1998			"Hamberg cohort"		All cancers SMR 180 ppt yr 1.07 988 1.64 3,416 1.33 10,425 1.64
Michalek et al 1998 (Mortality study)	Operation Ranch Hand Vietnam veterans 20 year follow-up	Agent Orange	US/Vietnam	SMR 1.3 "non-significant" for bronchus and lung	All cancer SMR 1.1
Mahan et al 1997 (Case control study)	Vietnam veterans with lung cancer compared with Vietnam veterans without cancer or with colon cancer	Agent Orange	US/Vietnam	OR 1.39 (95% CI 1.01-1.92) When adjusted by year of birth relationship disappeared	

Kogevinas et al 1997 (Mortality study)	n= 21,863 male and female workers exposed to phenoxy herbicides, chlorophenols and dioxins; 36 cohorts in 12 countries	phenoxy herbicides, chlorophenols and dioxins	12 countries	SMR 1.12 (95% CI 0.98-1.28) Rate ratio for workers exposed to TCDD or higher chlorinated dioxins = 1.29 (95% CI 0.94-1.76) compared with cohort exposed to phenoxy herbicides and chlorophenols with minimal/no exposure to TCDD	SMR all cancers 1.12 (95% CI 1.04-1.21)
Becher et al 1996 (Mortality study)	Phenoxy herbicides production, exposure to TCDD and higher chlorinated dioxins (n= 2,479)	Phenoxy herbicides contaminated with TCDD and higher chlorinated dioxins (furans)	Germany	SMR 1.54 (95% CI 1.15-2.02) for respiratory cancer	SMR all cancers 1.19 (95% CI 1.00-1.41)
Ott and Zober 1996			"BASF cohort"		All cancers SMR 605 ppt yr 0.80 19,614 1.20 55,645 1.40 150,454 2.00
Zober et al 1994 (Mortality study)	Chemical plant reactor accident	TCDD	Germany		Benign and unspecified neoplasms were marginally increased in highly exposed TCDD subgroups

Collins et al 1993 (Mortality study)	Trichlorophenol process accident n=754	TCDD	US	Those who developed chloracne (n=122) had “increased mortality rates from respiratory cancer” and others	
Coggon et al 1991 (Mortality study)	Chemical manufacture workers	Phenoxy herbicides, chlorophenols and dioxins	UK	Non-significant excess of lung cancer (19 observed, 14.2 expected)	
Fingerhut et al 1991 (Mortality study)	Chemical production workers (n=5,172 at 12 plants)	TCDD	US	SMR 1.42 (95% CI 1.03-130) for cancers of the respiratory system in subgroup with ≥1 year exposure and ≥1 20 year latency	All cancers SMR 1.15 (95% CI 1.03-1.92), All cancers SMR in subgroup with ≥1 year exposure and ≥1 20 year latency 1.46 (95% CI 1.21-1.76)
Thiess et al 1982 (Mortality study, 27 year follow up)	Trichlorophenol processing plant (n=74)	Dioxin	BASF plant, Germany	(Included bronchial cancer)	All cancer 7 observed, 4.1 expected
Pazderova-Vejlupková et al 1981	Chemical production plant (n=55)	TCDD		2 deaths from bronchogenic lung carcinoma	

Key: TCDD - tetrachlorodibenzo-p-dioxin; HR – hazard ratio; CI – Confidence Interval; SMR – standardised mortality ratio; PCP – pentachlorophenol; TCP – trichlorophenol; OR – odds ratio; ppt yr – parts per trillion per year.