

MATline: a job-exposure matrix for carcinogenic chemicals

Luisella Gilardi, Umberto Falcone, Silvano Santoro and Elena Coffano

DoRS, Centro di Documentazione per la Promozione della Salute, Regione Piemonte, Grugliasco, Turin, Italy

Summary. MATline is a tool that can be used to predict which industrial processes can be expected to involve the use of a substance that is considered carcinogenic as documented in the literature. The database includes agents carrying risk phrases R45, R49 and R40 according to the method of classification adopted by the EU and/or agents in categories 1, 2A and 2B as classified by the International Agency for Research on Cancer (IARC). Each agent is associated with a list of industrial processes coded according to the tariff headings used by the National Institute of Insurance against Occupational Injuries and Diseases (Istituto Nazionale per l'Assicurazione contro gli Infortuni sul Lavoro – INAIL). The main sources of information are the IARC Monographs and databases available through the National Library of Medicine's TOXNET portal. The matrix currently includes 600 carcinogenic agents, 23 classes of agents and some 7000 links between agents and industrial processes. MATline can be viewed on the www.dors.it website.

Key words: occupational exposure, databases, carcinogens.

Riassunto (*MATline: la matrice lavorazione-esposizione sulle sostanze cancerogene*). MATline, è uno strumento che consente di prevedere in quali attività lavorative ci si può attendere l'uso di una sostanza cancerogena sulla base della documentazione di letteratura. Gli agenti inclusi sono quelli classificati con frasi di rischio R45, R49, R40 dalla Comunità Europea e/o classificati nei gruppi 1, 2A e 2B dall'Agenzia Internazionale per la Ricerca sul Cancro (IARC). Ad ogni agente è stata associata una lista di lavorazioni codificate secondo il sistema di voci di tariffa dell'Istituto Nazionale per l'Assicurazione contro gli Infortuni sul Lavoro (INAIL). Le principali fonti utilizzate sono le Monografie della IARC e le banche dati accessibili tramite il portale TOXNET della National Library of Medicine. Attualmente sono presenti 600 agenti cancerogeni, 23 classi di agenti e circa 7000 incroci tra agente e attività economica. MATline è consultabile sul web all'indirizzo www.dors.it.

Parole chiave: esposizione occupazionale, basi di dati, cancerogeni.

INTRODUCTION

Earlier studies have found that, on average, 8.4% of all cancer deaths are attributable to work [1]. There are approximately two million work-related deaths each year. Worldwide, the largest groups of work-related diseases are cancers, circulatory diseases and communicable diseases. In the EME (established market economies) area 165 581 annual deaths due to cancer are work-related [2].

According to estimates by Carex, an international information system on occupational exposure, in Italy about 4.2 million workers, *i.e.*, 24% of the workforce, are exposed to carcinogens [3].

Prevention should start with elimination, banning, substitution, and any other measures aimed at minimizing the quantity and quality of exposure to carcinogenic substances and agents. This needs better occupational safety and health management systems at the enterprise level, strategies and national programs at the country and regional levels.

Risk management depends largely from the risk assessment process.

Risk assessment consists of a four-step process:

- a) hazard identification;
- b) effect assessment;
- c) exposure assessment;
- d) risk characterization.

The final step integrates the information collected in the previous three steps; that is it integrates the qualitative and quantitative information about the toxicological properties of the identified chemicals with the extent to which workers are exposed to them.

Worldwide, some agencies such as the US Environmental Protection Agency (USEPA), the US National Toxicology Program (US NTP), and the International Agency for Research on Cancer (IARC), seek to identify the causes of human cancer, and to evaluate them on the basis of the strength of the evidence for carcinogenicity arising from human and experimental animal data.

In particular the IARC, with the help of international working groups of experts, publishes Monographs, critical reviews and evaluations of evidence on the carcinogenicity of a wide range of human exposures. The Monographs represent the first step in carcinogen risk assessment, which involves examination of all relevant information in order to assess the strength of the available evidence that exposure to a certain agent could alter the age-specific incidence of cancer in humans [4].

Besides, the possibility of knowing *a priori* the companies where exposure to carcinogens is higher could be helpful in the exposure assessment step.

The job-exposure matrix (JEM) can be useful for this purpose; a JEM is a cross-classification of job titles/industries and exposures that allows exposure to be inferred on the basis of the job title or industry [5, 6].

The toxicological data of the chemical agents evaluated by the IARC and/or classified as carcinogenic by the European Union [7] are integrated with the list of industrial processes in which such agents are used or formed as by-products, in order to perform risk characterization and thus complete the risk assessment process.

In this framework the Documentation Service for Health Promotion of Piedmont Region in collaboration with the Industrial Hygiene group from the Environmental Protection Agency developed an information system which enables users to access the chemical agent database containing general information and carcinogenic classifications, and cross-reference each agent with the relative industrial processes.

MATERIALS AND METHODS

Inclusion of carcinogenic substances

The matrix includes the substances classified as carcinogenic under European legislation.

For that purpose, reference was made to the amendments to Annex 1 of Directive 67/548/EEC [7] listing substances with risk phrase:

- R40 possible risks of irreversible effects;
- R45 may cause cancer;
- R49 may cause cancer by inhalation.

Reference was also made to the IARC classification [4], according to which the substances included in the database are classified as follows:

- Group 1: the agent is carcinogenic to humans;
- Group 2A: the agent is probably carcinogenic to humans;
- Group 2B: the agent is possibly carcinogenic to humans.

The current version does not include substances developed or used as drugs and those for which human exposure is only via food consumption or limited to their non-essential use or natural occurrence, complex mixtures and metal alloys.

Definition of the fields to be completed for each agent

Each chemical substance data sheet must provide the following information:

- the main information to enable the agent to be

identified unambiguously;

- the specific chemical family to which it belongs;
- the main carcinogenicity classifications (IARC group, EC classification);
- specific carcinogenic activity in humans, when demonstrated, or in animals;
- specific use and industries in which the agent may be present in the form of a raw material, semi-finished product, contaminant or finished product;
- threshold limit values for exposure at work;
- BEIs (Biological Exposure Indices);
- sources of information;
- date of last change (last modified).

Links with industrial processes

On the basis of data from the literature taken from the "Uses" and "Occupational exposure" chapters of the IARC Monographs and/or from the "Major uses" section of the Hazardous Substances Data Bank [8] each agent was associated with the list of industrial processes in which it might be present.

Each industrial process was coded according to the tariff headings of the National Institute of Insurance against Occupational Injuries and Diseases (INAIL) [9].

Updating

The database is updated on a regular basis. Data concerning classifications and labelling are updated every six months to bring them in line with the latest amendments to Annex 1 of Directive 67/548/EEC. The IARC Monographs are consulted regularly in order to update the information on carcinogenicity classifications, target organs, uses and types of industry.

The Threshold Limit Values and Biological Exposure Indices are updated once a year on the basis of reviews and amendments proposed by the American Conference of Governmental Industrial Hygienists (ACGIH) [10].

The "last modified" field on each data sheet informs the user when the information was last updated.

Access

MATline can be accessed free of charge via the website www.dors.it/matline/matline.php.

Pages use PHP and the database is developed on the MYSQL platform, which can be updated by qualified technicians using dynamic web pages.

Methods of evaluation

To understand how and to what extent MATline provides the information its users require and to obtain information about the characteristics of its users, between February and July 2005 all those who logged on to the MATline site were invited to take part in a six-question survey.

Other data on the use of the website were gathered automatically starting on 1 January 2005. We created a log of each single access and path through the pages of the site. This log formed the basis for obtaining detailed access statistics.

In order to further evaluate the validity of the information available through MATline, a field study was carried out in 2006 to verify the actual presence of the carcinogenic agents that, according to the matrix, could be expected to be found in a specific sector, namely the galvanizing industry. This assessment was performed by working in collaboration with the Industrial Hygiene department of ARPA Piemonte on its project called "Prevenzione nel comparto galvaniche del Piemonte Nord-Orientale" (Prevention in the galvanizing industry in north east Piedmont). The project involved 82 companies in the sector [11]. Further assessments concerning other specific industry sectors are currently underway.

RESULTS

MATline is currently able to offer users up-to-date and consultable data sheets on 23 agent classes, 602 substances included by the IARC and EU and with the potential for use in industry.

More specifically, data sheets are available for 102 chemical substances in class 1 (known carcinogens), 77 substances in class 2A (probable carcinogens), 247 in class 2B (possible carcinogens), 51 in class 3 (not classifiable for human carcinogenicity) and 99 classified by the EC only.

Of all the data sheets available, 285 report TLV-TWA values for 2006, based on those defined and revised annually by the ACGIH [10], 450 data sheets also include the target organ of the agent's carcinogenic activity. As for the industrial process fields on each data sheet, the matrix refers to 437 INAIL codes, giving rise to 7318 combinations with the various chemical substances (Table 1).

Users can access information in three different ways, depending on whether they know the name or CAS number of the agent (search by agent), the type of industrial process (search by process) or the target organ of the cancer that developed following

occupational exposure (search by target organ). In all cases, the search leads to the production of the "Complete data sheet for the carcinogenic agent".

MATline is a flexible and user-friendly tool that can even be used by those with no specific experience in the field. Agents are also grouped at an additional level so that information can be obtained simply by typing commonly used terms or chemical terms that are not strictly correct in the search box. For example, the user can enter the term "bitumen" to open a page with a discursive description of the general chemical and toxicological properties of this "class". This page also contains a list of all the associated agents (bitumen emulsion, blended or fluxed bitumens, asphalt, cutback bitumens, etc.) with links to the relative data sheets. This type of search is also possible for other "classes" including welding fumes, mycotoxins, tar, gasoline, mineral oils, etc.

Evaluation

The access log enabled us to obtain the following information for 2005, 2006 and the first half of 2007.

The number of users rose slightly throughout the period considered: 7205 users in 2005, 7253 in 2006 and 3179 in the first six months of 2007. There was a more marked increase in the number of pages visited, with a total of 63 779 in 2005, a total of 81 550 in 2006 and 39 133 in the first six months of 2007 (Figure 1).

The breakdown of data for 2006 shows that 17 807 searches were performed using the matrix's internal search engine, with an average of 19 users per day, 223 pages visited and 48.8 searches. Thus, on average, each user visited 12 database pages per day.

The most frequent searches were by single agent (78%), free text searches, CAS number and alphabetical list. As regards the other search methods, 13.6% of users searched for substances by industrial process and 8.6% by target organ.

Seventy-five users completed a voluntary online questionnaire, which provided the following results.

The search engine (39%) and links from other sites (32%) were the preferred paths for users accessing the database.

More than 50% of those who completed the questionnaire worked for professional firms or privately-held concerns, 64% of participants said they frequently found the information they were looking for. Around 50% required information for the purpose of professional development and used the data to supplement other sources of information.

The validity of the information obtainable using MATline was further assessed by comparing it with data collected during a field study by the Industrial Hygiene Department of ARPA Piemonte as part of the project called "Prevenzione nel comparto galvaniche del Piemonte Nord-Orientale" (Prevention in the galvanizing industry in north east Piedmont) [11]. The comparison between the list of substances obtained through MATline for the specific class (galvanic technology) and the list of substances recorded by

Table 1 | Summary of the information available in the MATline database

Contents of MATline	Number
Carcinogenic chemical agents included	602
Group 1 agents according to the IARC classification	102
Group 2A agents according to the IARC classification	78
Group 2B agents according to the IARC classification	247
Agents classified by the EC (R 40; R 45; R 49) and as group 3 by IARC	50
Agents classified by the EC only (R 40; R 45; R 49)	99
Chemical agents with TLV-TWA values	285
Chemical agents with indication of the target organ	450
INAIL industrial process codes included	437
INAIL code – chemical agent combinations	7318
Synonyms	7087
Carcinogen classes included	27

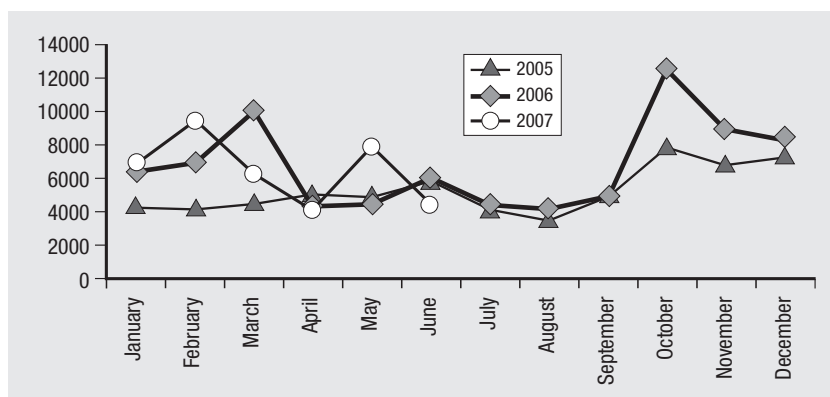


Fig. 1 | Graph of accesses to MATline over the three-years period 2005 – June 2007.

ARPA with a volume of use equal to or greater than 100 kg per year showed a 36% correspondence.

DISCUSSION

There are numerous resources available online for identifying and assessing the risk associated with hazardous chemical agents but, although exhaustive and reliable, most are in English and refer to American legislation [12].

MATline can be accessed via the web at no charge and is available in Italian. The information is concise and readily accessible to satisfy the needs of users who want to be able to identify and assess the effects of carcinogenic agents quickly.

The access log for the last three years shows a moderate but constant increase in the number of pages visited.

Furthermore, MATline can be used to predict which industrial processes can be expected to involve the use of a substance that is considered carcinogenic as documented in the literature. It includes the industrial sector codes used by INAIL so that users can link directly to the company archive available from each of the Workplace Safety and Prevention Units (SPreSAL) in Piedmont.

This information can be used to create risk maps and pinpoint priority areas in which to implement suitable measures in order to eliminate or reduce the risk.

There are however certain limits that must be considered in order to ensure the correct use of MATline. Information on industrial uses is taken from bibliographic sources and the uses and industrial processes described may therefore not always reflect the technological state of the art and industrial context in Italy.

References

1. Nurminen M, Karjalainen A. Epidemiological estimate of the proportion of fatalities related to occupational fraction in Finland. *Scan J Work Environ Health* 2001;27:161-3.
2. Hamalainen P, Takala J, Saarela KL. Global estimates of fatal work related diseases. *Am J Ind Med* 2007;50:28-41.
3. Mirabelli D. Estimated number of workers exposed to carcinogens in Italy, within the context of the European study CAREX. *Epidemiol Prev* 1999;23:346-59.
4. International Agency for Research on Cancer. *IARC Monographs on the evaluation of carcinogenic risks to humans*. Vol. 1-88. Lyon, France: IARC; 2007. Available from: <http://monographs.iarc.fr/>.
5. Acheson ED. What are job exposure matrices? In: Medical Research Council, Environmental Epidemiology Unit. *Job exposure matrices: Proceedings of University of Southampton Conference*. April 1982. Southampton: Southampton General Hospital; 1983. (Scientific Report, n. 2). p. 1-4.

The substances included may no longer be in use or may be used in situations that are not the same as those described. Since exposure to the various carcinogenic agents is assigned on the basis of bibliographic sources rather than from actual observations, it should be regarded as potential exposure.

This limit has been overcome, albeit only in part, by working in partnership with ARPA on the galvanizing industry project. The two lists do not completely match, but the agents included in the MATline database are those typical of the industry, to which exposure is more frequent and more intense.

We are currently working with ARPA on another project to validate and integrate data for the metal-working industry.

There are also plans to include a link to the site of the European Chemicals Agency in Helsinki set up under the new chemicals regulation that came into force in Italy and the whole of Europe on 1 June 2007 [13].

CONCLUSION

Despite its limits, MATline can be used to satisfy a variety of needs for information, and most importantly as a reliable tool to assess the risk associated with the use of carcinogenic agents.

However, the data from the literature must be integrated with the results of *ad hoc* studies. The database must take into account the actions envisaged by the new REACH regulation on chemicals and improve its feedback capabilities as far as its actual use is concerned.

Submitted on invitation.

Accepted on 16 December 2007.

6. Bouyer J, Hemon D. Retrospective evaluation of occupational exposures in population-based case-control studies; general overview with special attention to job exposure matrices. *Int J Epidemiol* 1993;22(Suppl. 2):S57-S64.
7. Council of the European Economic Community. Council Directive 67/548/EEC of 27 June 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances. *Official Journal of European Communities L* 196, 16/8/1967.
8. National Library of Medicine. *Toxicological data network*. Available from: www.toxnet.nlm.nih.gov; last visited 21/11/2007.
9. Istituto Nazionale per l'Assicurazione contro gli Infortuni sul Lavoro. *Tariffe dei premi con repertori analitici*. Roma: INAIL; 2001.
10. Associazione Italiana degli Igienisti Industriali. Threshold limit values, biological exposure indices, ACGIH 2006 and EU threshold limit values. *Giornale Igienisti Industriali* 2006;31(Suppl.):1-237.
11. Arpa Piemonte, Centro Regionale per l'Epidemiologia e la Salute Ambientale – SS 20.02 Igiene Industriale. *Piano di intervento mirato alla riduzione dei rischi professionali nel comparto galvaniche del Piemonte Nord-Orientale*. Torino: Arpa; 2006.
12. Gilardi L, Fubini L, Bongiovanni P, Dalmaso M. Fonti informative per valutazione rischio chimico: le banche dati consultabili tramite internet. *Giornale Igienisti Industriali* 2000;25:143-52.
13. European Parliament and the Council of the European Union. Regulation (EC) n. 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the registration, evaluation, authorization and restriction of chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) n. 793/93 and Commission Regulation (EC) n. 1488/94, as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/CE and 2000/21/EC. *Official Journal of the European Union L* 396, 30/12/2006.