Introduction

History of the NORA process and framework for the meeting
by Paul A. Schulte

This is a concerted effort to identify means of reducing the insufficiency of available data for classifying particular agents in the International Agency for Research on Cancer (IARC) system by identifying information needs and gaps and the research to address them for 20 selected agents generally, in IARC categories 2A, 2B, and 3.

This project originated as part of the National Institute for Occupational Safety and Health's (NIOSH) National Occupational Research Agenda (NORA) to enhance occupational cancer research. The project ultimately involved collaboration with IARC, the National Institute of Environmental Health Sciences (NIEHS), the American Cancer Society (ACS), and the National Cancer Institute (NCI). The planning group consisting of Kurt Straif and Vincent Cogliano (IARC), Paul Schulte, Tania Carreón-Valencia, Avima Ruder, Mary Schubauer-Berigan (NIOSH), Ruth Lunn (NIEHS), Nat Rothman (NCI), and Elizabeth Ward (ACS) selected 20 agents, reviewed in previous IARC Monographs, on the basis of potential for workplace or environmental exposure, and importance or interest by a particular agency.

The purpose was two-fold: (1) identify research needs to address the information needs and gaps for a more definitive classification, and (2) Create a report that will be of value to funding agencies in determining possible projects to support.

The selected experts, generally two for each agent (one toxicologist and one epidemiologist), who either had participated in an IARC Monograph working group that addressed a candidate agent or who were knowledgeable about one or more agents, were selected by the planning committee. For each agent, the experts used a systematic approach reviewing the Monograph and the literature published since the Monograph meeting to determine whether potential research gaps and needs still existed, and what research was needed to change the classification. In addition, experts were encouraged to identify research in progress that they were aware of that could possibly affect the gap analysis.

For each agent, a common reporting template was used. All templates had the following categories:

- Summary
- Citation for most recent IARC review
- Current evaluation
- Exposure and biomonitoring
- Cancer in humans
- Cancer in experimental animals
- Mechanisms of carcinogenicity
- Research needs and recommendations
- Selected relevant publications since IARC review / References

The focus of the recommendations was not meant to be a compilation of all useful or interesting research but rather a focus on research that would be critical or important in resolving classification uncertainties. These templates were uploaded and shared among the experts before the meeting, and discussed during the meeting. Afterwards the templates were revised reflecting the discussions in the meetings. The templates vary in length depending on available new cancer research conducted on the carcinogenic agent since the last IARC update. These revised templates are compiled here to make this comprehensive technical report. The results of this meeting are published in this extensive technical report published by IARC, and in summary format as an article in the Environmental Health Perspectives.

Resolving the Carcinogenicity of Agents in IARC Groups 2A and 2B: Identification of High-Priority Research

by Vincent Cogliano

Common interests of IARC and NORA are to identify research that could lead to a more definitive classification for suspected carcinogens whose classification is now unresolved (e.g. in IARC Groups 2A or 2B). This could lead to well-planned epidemiologic or mechanistic studies, followed by a more definitive classification (either higher or lower) for these agents.

The previous NORA–IARC workshop (Sept 2006) was charged with considering current data for agents in IARC Groups 2A, 2B, or 3. These agents were then sorted into three groups:

- Agents that could be in Group 1 now and should be considered for Volume 100 of the *IARC Monographs*, which is updating the assessments of the more than 100 agents classified in Group 1;
- Agents for which new research is likely to change the classification and should be considered for NORA priority list; and
- Agents for which new research is not likely to change the classification and should be dropped as a NORA priority.

Overview of IARC's evaluation process

The *IARC Monographs* are a series of scientific evaluations developed by international working groups of expert scientists. Periodically, IARC convenes advisory groups to advise on priorities for future evaluation or reevaluation (IARC 2003). Agents are selected for evaluation based on evidence of human exposure and some evidence or suspicion of carcinogenicity. Each year, IARC generally convenes three separate working groups on different topics. Meetings are announced on the Internet about one year in advance, accompanied by a Call for Data (IARC 2004). Two principles govern the selection of working group members: to invite the best qualified experts, and to avoid real or apparent conflicts of interest.

There is a standard structure of the Monographs, where the first four sections provide a critical review of the pertinent scientific literature, and the final sections include summaries of the scientific data and the evaluations developed by the working group. The working group develops its evaluations through a series of distinct steps; providing insight into the working group's reasoning by revealing the weight given to each line of evidence.

The evidence of cancer in humans and cancer in experimental animals has four descriptors: "sufficient evidence," "limited evidence," "inadequate evidence," or "evidence suggesting lack of carcinogenicity" (for definitions of these terms, see IARC 2006). These two partial evaluations are combined into a preliminary default evaluation that the agent is "carcinogenic to humans" (Group 1), "probably carcinogenic to humans" (Group 2A), "possibly carcinogenic to humans" (Group 2B), "not classifiable as to its carcinogenicity to humans" (Group 3), or "probably not carcinogenic to humans" (Group 4) (Figure 1).

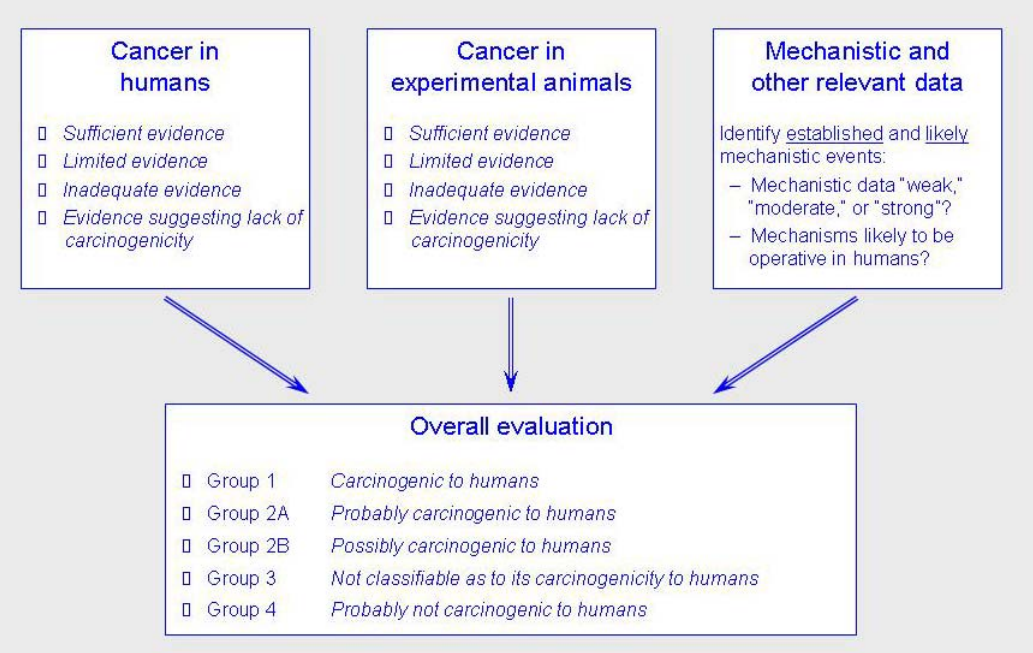

Figure 1 Overview of IARC's evaluation process

For example to reach *sufficient evidence* of carcinogenicity, as stated in the Preamble (IARC 2006): the Working Group considers that a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence.

To reach an evaluation in IARC Group 1: *Carcinogenic to humans*, as stated in the Preamble (IARC 2006): This category is used when there is sufficient evidence of carcinogenicity in humans. "Exceptionally, an agent may be placed in this category when evidence of carcinogenicity in humans is less than sufficient but there is sufficient evidence of carcinogenicity in experimental animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity."

The mechanistic and other relevant data are considered to determine whether the default evaluation should be modified (figure 2). This determination considers the strength of the mechanistic evidence and whether the mechanism operates in humans. The final overall evaluation is a matter of scientific judgment, reflecting the weight of the evidence derived

from studies in humans, studies in experimental animals, and mechanistic and other relevant data.

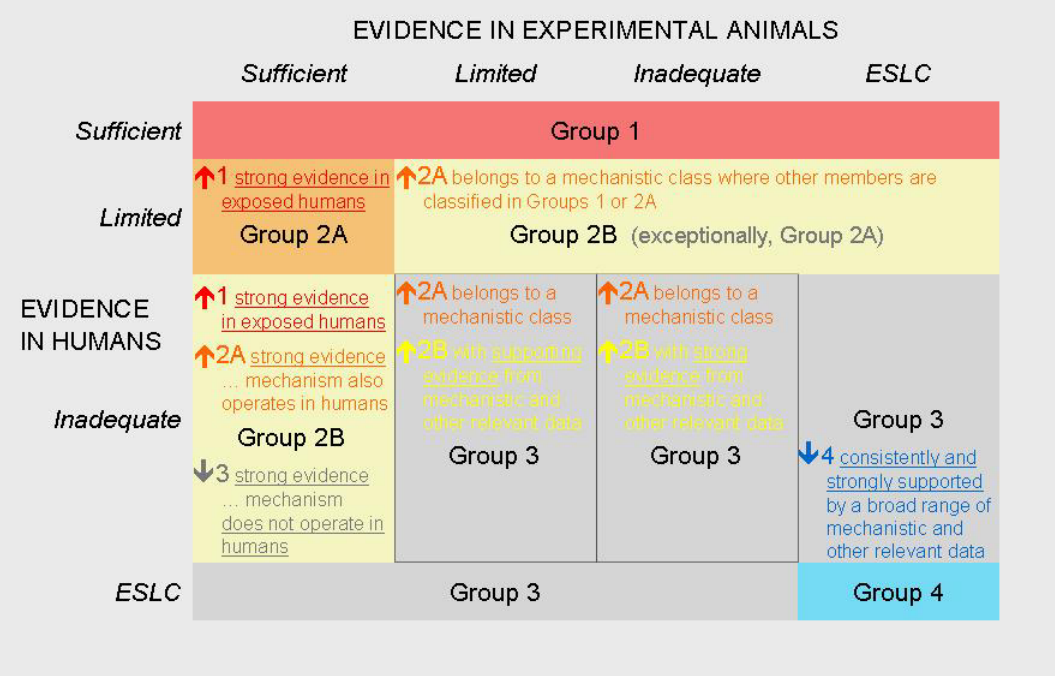

Figure 2. Mechanistic data can be pivotal when the human data are not conclusive

The NORA-IARC workshop 2009 was charged with two tasks:

- for each NORA priority agent where epidemiologic studies may yield sufficient evidence in humans, include human cancer studies in the research plan
- for each NORA priority agent where mechanistic studies may yield "strong evidence in exposed humans," include mechanistic studies in the research plan

This technical report list the agents for review in the following order: Inorganic agents such as metals (lead and lead compounds, indium phosphide, cobalt metal, titanium dioxide), metal fumes (welding fumes), fibers (refractory ceramic fibers), and particles (diesel engine exhaust, carbon black), followed by organic agents such as oxides (styrene, styrene oxide, propylene oxide), aldehydes (formaldehyde, acetaldehyde), chlorinated solvents (trichloroethylene, tetrachloroethylene, dichloromethane, chloroform, PCB), plasticizer (DEHP), and pesticide (atrazine), and lastly, shift work.

IARC-Classified Agents Selected for Review

Agent	Year of Monograph	Volume	Human evidence	Animal evidence	Overall evaluation
Formaldehyde	2006	88	S	S	1
Lead and lead compounds	2006	87	L	S	2A
Indium phosphide	2006	86	I	S	2A
Shiftwork that involves nightwork	2007	98	L	S	2A
Cobalt metal with tungsten carbide	2006	86	L	S	2A
Diesel engine exhaust	1989	46	L	S	2A
Clorinated solvents					
Styrene-7,8-oxide	1994	60	I	S	2A
Trichloroethylene (TCE)	1995	63	L	S	2A
Tetrachloroethylene (PERC)	1995	63	L	S	2A
Polychlorinated biphenyls (PCB)	1987	18	L	S	2A
Styrene	2002	82	L	L	2B
Propylene oxide	1994	60	I	S	2B
Acetaldehyde	1999	71	I	S	2B
Dichloromethane (DCM)	1999	71	I	S	2B
Chloroform	1999	73	I	S	2B
Di-2-ethylhexyl phthalate (DEHP)	2000	77	I	S	3
Atrazine	1999	73	I	S	3

I = Inadequate evidence; L = Limited evidence; S = Sufficient evidence