

# SECTION OF ENVIRONMENT AND RADIATION (ENV)

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Central to ENV is investigation of external environmental exposures, such as pollutants and occupational exposures. One major area of interest is pesticides, with current research on cancer risk in cohorts of agricultural workers and pesticide applicators. Using studies on testicular cancer in France and in the Nordic countries and pooled analyses of studies of childhood leukaemia, ENV is looking at the risk of haematological diseases in these populations and the cancer risk in the offspring of exposed farmers. Other substantial efforts include identifying occupational risk factors for lung cancer, with a focus on the effects of occupational carcinogens, such as asbestos and silica, and of smoking. Lifestyle-related questions are part of comprehensive studies of cancer when there is potential interaction between environmental and other factors. Such studies, for example those initiated in sub-Saharan African countries, focus on breast, oesophageal, and childhood cancers.

ENV is also involved in many projects related to ionizing radiation, including the effects of protracted low doses of external ionizing radiation from medical diagnostic examinations (e.g. cohort study of children and adolescents exposed to computed tomography) and from occupational activities (e.g. followup of workers in the nuclear industry); environmental studies of populations exposed to fallout from the Semipalatinsk nuclear test site or after the Chernobyl nuclear accident; collaboration in studies on in utero exposure to ionizing radiation in the Southern Urals; and studies on the interaction between ionizing radiation and genetic factors, such as thyroid cancer in young people. Collaborations on studying the long-term effects from the Chernobyl nuclear accident are currently under way with colleagues from Fukushima Medical University. With regard to non-ionizing radiation, research activities include investigations of mobile phone use and studies on extremely low-frequency magnetic fields and childhood cancer.

Translating research into prevention policy is particularly important for environmental risk factors, many of which are modifiable. ENV has a large role in IARC's update of the European Code Against Cancer, which makes recommendations of what actions to take to improve general health and reduce the risk of cancer.

# THYROID CANCER AFTER RADIATION EXPOSURE IN ADULTHOOD

While there is evidence that the risk of thyroid cancer after radiation exposure substantially decreases with increasing age of exposure, lower risk is not equal to no risk. This view was strengthened by a recent IARC study of Chernobyl clean-up workers from Belarus, the Russian Federation, and Baltic countries (Kesminiene *et al.*, 2012), which reported an increase in the risk of thyroid cancer after radiation exposure during the clean-up activities in the Chernobyl area:

the excess relative risk (ERR) per 100 mGy was 0.38 (95% confidence interval, 0.10–1.09). The data from the Chernobyl accident provide a valuable opportunity to clarify the risk of thyroid cancer after adult exposure and to plan for responses to nuclear accidents, like the 2011 disaster at the Fukushima Daiichi nuclear power plant, since adults will be responsible for clean-up and remediation activities after any accident.

## Occupational risk factors of lung cancer: the SYNERGY consortium

The SYNERGY project compiles the world's largest database of case-control studies on lung cancer with detailed information on occupation and smoking. The main objectives are to estimate risks at low exposure levels that are relevant for the general population and to estimate joint effects of selected occupational exposures and smoking in the development of lung cancer. The detailed smoking data allow for adjustment by smoking status, and the large data set permits risk estimates in important subpopulations, such as women and never-smokers, as well as by lung cancer cell type. The association between exposures or jobs and lung cancer risk often varies by lung cancer cell type. Although this has rarely been studied before due to small sample sizes, it is important to correctly estimate risks by lung cancer cell type especially when revising threshold levels and establishing compensation schemes for exposed workers and their families.

SYNERGY focuses on exposure to asbestos, silica, chromium, nickel, and polycyclic aromatic hydrocarbons. Collaborators have developed a quantitative job-exposure matrix (SYN-JEM) based on actual exposure measurements (360 000) from multiple countries covering a period of more than 50 years. Different model specifications have been compared to predict historical job-, time, and region-specific exposure levels in the best possible way. Exposure levels have been calculated for each subject by linking the SYN-JEM with the individual occupational histories.

Several other research questions have been addressed in SYNERGY, including whether working in specific jobs – such as hairdresser, welder, baker, bricklayer, or cook – can increase the risk of lung cancer (Table 1). In one study, an increased risk of lung cancer was observed for female

Table 1. Association between working in certain occupations and the risk of lung cancer from pooled analyses of case-control studies participating in the SYNERGY project

Reference	Population	Exposure	Odds ratio 1 (95% confidence interval)ª	Odds ratio 2 (95% confidence interval) <sup>ь</sup>
Behrens <i>et al.</i> , 2013	Men	Ever employed as baker	-	1.08 (0.90–1.31)
Behrens <i>et al</i> ., 2013	Women	Ever employed as baker	-	0.96 (0.47–1.97)
Kendzia <i>et al.</i> , 2013	Men	Ever employed as welder	1.69	1.44 (1.25–1.67)
Kendzia <i>et al.</i> , 2013	Men	Longest held job including occasional welding	1.37	1.32 (1.17–1.49)
Olsson <i>et al.</i> , 2013	Men	Ever employed as men's hairdresser/ barber	1.17 (0.84–1.61)	1.09 (0.76–1.59)
Olsson <i>et al.</i> , 2013	Women	Ever employed as women's hairdresser	1.65 (1.16–2.35)	1.12 (0.75–1.68)

<sup>a</sup> Odds ratio 1 without adjustment for tobacco smoking habits.

<sup>b</sup> Odds ratio 2 with adjustment for tobacco smoking habits.

hairdressers, which decreased and became non-significant after adjusting for smoking habits; thus, our results suggest that the increased lung cancer risk was due to their smoking behaviours rather than their occupational exposures (Olsson et al., 2013; Figure 1). However, a few female hairdressers employed before 1954 had an increased risk even after adjustment for smoking. Similarly, we observed that, in general, cooks did not experience an increased risk of lung cancer after adjustment for smoking (Behrens et al., 2013). Welding was associated with an elevated lung cancer risk, among both full-time and occasional welders, and the risk increased with duration of employment. In welders, a stronger association was observed with lung cancer in never-smokers and light smokers and with squamous cell lung cancer and small cell lung cancer, but not with adenocarcinoma. Thus, our findings contribute to the increasing evidence that welding is associated with an increased risk of lung cancer (Kendzia et al., 2013). We did not observe an increased lung cancer risk in baking-related professions. Bricklayers experienced an increased lung cancer risk, with a clear increasing trend with length of employment. This is of importance because the association between working as a bricklayer and increased lung cancer risk has not vet been firmly established. In most countries, therefore, lung cancer is not usually recognized as an occupational disease among bricklayers and the affected workers are not compensated. SYNERGY provides additional evidence of increased lung cancer risk among bricklayers, which may contribute to it being considered an occupational disease.

# $\begin{array}{l} C \\ \text{Ancer in Agricultural Workers:} \\ \text{The AGRICOH consortium} \end{array}$

Coordinated by ENV, AGRICOH is a consortium of at present 27 agricultural cohort studies from 11 countries in five continents. Launched in October 2010 in Lyon, AGRICOH promotes pooling of data to study health outcomes associated with agricultural exposures, in particular pesticides, to increase statistical power to study rare diseases (e.g. ovarian, testicular, and thyroid cancers) or uncommon exposures (infrequently applied chemicals), and to replicate

Figure 1. An increased risk of lung cancer among hairdressers has been reported, but the SYNERGY study proposes that this is due to their smoking behaviour and not to workplace chemicals. © IARC/R. Dray.



findings from individual studies. About half of the cohorts in the consortium collect data on cancer incidence and mortality. The consortium has met in 2011 and 2013 in Barcelona and Utrecht, respectively.

The first pooling project within AGRICOH, led by ENV, is on the risk of lymphomas, leukaemias, and multiple myelomas in association with exposure to pesticides. This 2-year project uses information on crops farmed during different time periods in combination with external data to generate crop-exposure matrices and determine exposure to pesticides when data on chemical exposures were not directly collected. The project is assessing exposure to 17 chemical groups and more than 25 specific active ingredients in approximately 350 000 farmers from France, Norway, and the USA. This study will be completed by November 2014.

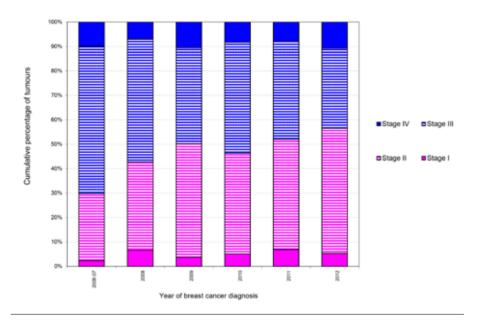
ENV and the United States National Cancer Institute are developing a second project to describe cohort-specific cancer burden within the studies included in the consortium. Crude incidence and mortality rates of cancers of all types, as well as age-standardized and gender-specific incidence and mortality rates, will be the main outcomes of this investigation. AGRICOH cohorts joining this project are from Australia (n = 2), France (1), Norway (3), the Republic of Korea (1), and the USA (2). Completion of this study is expected during 2014.

### $Breast\, {\rm cancer}\, {\rm in}\, {\rm sub-Saharan}\, Africa$

Breast cancer in sub-Saharan Africa is characterized by disproportionately low survival rates, which, in light of projected increases in the incidence over the coming decades, warrant investigation to determine the relative contributions of biological, health system, and individuallevel factors, and for which a strong evidence base in this region is needed. ENV has developed a successful collaboration with the Chris Hani Baragwanath Academic Hospital breast clinic (Soweto, South Africa) based on its unique resource of high-quality clinical information on a large breast cancer case series of more than 1200 patients. To date, the work has revealed findings that are especially relevant to this and similar settings. For example, our research has shown that stage at diagnosis has improved during 2006-2012 within this public sector setting (Figure 2); that residential distance from the hospital is associated with later stage at diagnosis even within a small (20 km) radius; and that the prevalence of receptor-specific subtypes is dominated by disease subtypes with better prognosis, with agespecific estrogen receptor prevalence similar to that in African women aged 50 years or older (McCormack *et al.*, 2013a). These findings indicate that improvements in survival may be a realistic goal in this region. In addition, we have reported the high proportion (17%) of HIV-positive breast cancer patients at this hospital, which reflects the population-level HIV prevalence and the need to investigate treatment implications (Cubasch *et al.*, 2013).

As an extension of the above-mentioned work, we are partnering with the South African National Cancer Registry and Namibian and Botswanan collaborators to examine the epidemiology of breast cancer subtypes in a wider Southern African effort, the largest of its kind to date. We are also conducting the first general population study of mammographic density, a strong intermediate risk factor for breast cancer, in cooperation with the Pink Drive mobile mammography vans, which provide free mammograms to disadvantaged communities in South Africa (Figure 3).

Recently, ENV initiated the African Breast Cancer – Disparities in Outcomes (ABC-DO) study, funded by the Susan G. Komen foundation and conducted in collaboration with the London School of Hygiene and Tropical Medicine. ABC- Figure 2. Relative distribution of stage at breast cancer diagnosis by year of diagnosis at the Chris Hani Baragwanath Breast Cancer Clinic (Soweto, South Africa). Source: McCormack *et al.* (2013a); reproduced with permission from the publisher.



DO is a prospective follow-up study of 1800 newly diagnosed breast cancer patients at four public hospitals in South Africa, Namibia, Uganda, and Nigeria. Information will be collected on the entire breast cancer journey leading up to and for up to 3 years after diagnosis. ABC-DO will provide data on the proximal biological factors that are hypothesized to have a direct impact on survival – clinical factors at diagnosis, treatment received, and lifestyle/morbidity factors - as well as distal factors (e.g. health practices, socioeconomic status, cultural beliefs, and education). Given the growing prevalence of mobile phone use in Africa, follow-up methods will be based primarily on telephone interviews to overcome losses to follow-up seen in previous studies. The perspective of ABC-DO is that comparisons of breast cancer survival within Africa (i.e. between settings with similar resources, none of which have general population breast cancer screening) will provide more informative insights than comparisons outside the continent. These comparisons will identify settings with better survival prospects and the reasons for them.

# DIAGNOSTIC RADIATION AND RISK OF CHILDHOOD CANCER: THE EPI-CT STUDY

Medical exposure represents the largest man-made source of ionizing radiation exposure and has roughly doubled over the past two decades, mainly due to the growing use of computed tomography (CT) examinations. CT scanning in children and adolescents is of particular concern in radiological protection and public health, as studies of atomic bomb survivors and other populations indicate that children are generally more sensitive to the health effects of radiation than are adults. In addition, recent studies in

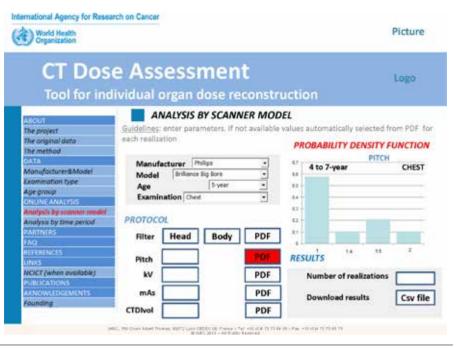
Figure 3. Pink Drive mobile mammography vans provide free mammograms to disadvantaged communities in South Africa. © IARC/Valerie McCormack.



the United Kingdom and Australia have reported an increased risk of cancer associated with paediatric CT scans. However, direct estimation of the health impact of radiation from CT scans remains imprecise since, in both studies, ascertainment of radiation doses was performed not at the individual level but by using group-average approaches.

A large European cohort of children who had CT examinations (EPI-CT) is currently being assembled by ENV to enrol more than a million patients from Belgium, Denmark, France, Germany, Netherlands, Norway, the Spain, Sweden, and the United Kingdom. Data collection started in October 2011 and will continue through the end of 2013; about 77% of the cohort has already been accrued. Data collection is split into two time periods - before and after introduction of the Picture Archiving Communication System (PACS) (Thierry-Chef et al., 2013). Before PACS, only sparse information about scanner settings, which is essential for reconstructing individual doses, was available from radiology departments. Hence, a multilevel approach was developed to retrieve information from questionnaire, surveys, scientific а publications, and expert interviews. For the years after PACS was introduced, an innovative approach was proposed to automatically extract the information

Figure 4. Entry screen of dose assessment for a study on cancer risk in children undergoing computed tomography (CT) examinations.

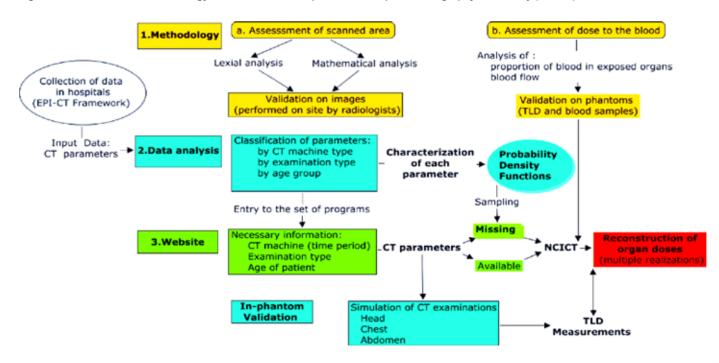


on scanner settings and mathematical descriptions of the contours of exposed organs, allowing mapping to the hybrid computational phantoms and faster automatic reconstruction of individual doses (Figure 4).

EPI-CT also pilot tested a collection of biological samples to assess various biomarkers (microarray gene expression studies, DNA damage by scoring  $\gamma$ -H2AX, and chromosomal aberrations)

of exposure related to the biological mechanisms behind the low-dose hypersensitivity observed in paediatric patients exposed to CT (Figure 5). The data collected on the patients is a very important starting point for assessing radiology practices and analysing ways to most effectively administer doses. A separate working group was therefore set up to explore how to optimize the use of paediatric CT procedures and redefine quality criteria for paediatric images.

Figure 5. Dose reconstruction strategy for the international paediatric computed tomography scan study (EPI-CT).

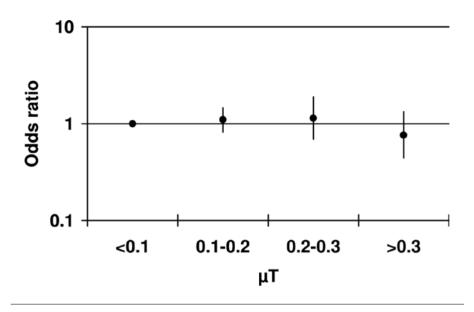


The EPI-CT study is unique because of its size, sophisticated dosimetry, and the attention being paid to identify, characterize, and take into account factors that may bias any possible association between the dose from CT scans and cancer risk. This includes, among others, missing CTs and confounding by socioeconomic status and by indication for the CT. It will provide more comprehensive and precise estimates of risk than those available to date, and will strengthen the scientific evidence about the effects of low-dose radiation exposure in young people.

The need for physicians to be cautious when recommending diagnostic procedures involving exposures to ionizing radiation early in life is strengthened by the conclusions of the GENE-RAD-RISK study, which found that ionizing radiation delivered in the course of diagnostic procedures to the chest before the age of 30 years may nearly double breast cancer risk in women who carry a mutation in the *BRCA1* or *BRCA2* gene (Pijpe *et al.*, 2012).

# Electromagnetic fields and risk of cancer

Scientific evaluations classify both extremely low-frequency magnetic fields (ELF-MF) (e.g. resulting from distribution and use of power transmission) and radiofrequency electromagnetic fields (RF-EMF) (e.g. from wireless communication) as possibly carcinogenic to humans (IARC Monograph classification Group 2B), indicating a need for further research. In 2001, ELF-MF was classified as Group 2B, and while epidemiological evidence suggests a weak association for childhood leukaemia, experimental studies failed to find a mechanism of action. Under the hypothesis that ELF-MF may promote growth of leukaemia cells, it was proposed that ELF-MF exposure could also be a risk factor for recurrence of disease. A multinational collaboration was initiated to investigate the relationship between ELF-MF and survival and risk of relapse in more than 3000 children with leukaemia from six countries, followed up for 10 years after diagnosis (Schüz et al., 2012). No association was seen, providing no evidence that ELF-MF has a role in predicting the outcome of childhood leukaemia (Figure 6). Due to Figure 6. In an international pooled analysis, no increase in mortality was reported with increasing exposure to residential extremely low-frequency magnetic fields (ELF-MF) in children with acute lymphoblastic leukaemia. Pooled odds ratios and their 95% confidence intervals (vertical axis) are shown by increasing levels of exposure to ELF-MF (reference category, < 0.1  $\mu$ T). Figure compiled from Schüz *et al.* (2012).



the widespread use of mobile phones, investigations into brain tumour risk in relation to mobile phone use are more topical. Studies to date are inconsistent; although they do not suggest an overall risk increase, among heavy mobile phone users an increased risk cannot be ruled out. In addition, mobile phones are a recent technology and longer observation periods are needed (Figure 7). Time trend analyses of glioma, an often malignant type of brain tumour, in the high-quality cancer registries of the Nordic countries did not suggest any incidence increase in mobile phone users (Deltour *et al.*, 2012), confirming the lack of an overall risk increase (Figure 8). An analysis within the prospective United Kingdom Million Women study, including 800 000 middle-aged women, did not

Figure 7. Although there is little evidence that mobile phone use increases the risk of cancer, more research is needed in very heavy users, for exposure durations longer than 20 years, and in users who start at a young age. Photograph courtesy of Florentina Kindler.



show any association of mobile phone use with glioma or meningioma, but an association with acoustic neuroma remained a possibility (Benson et al., 2013). Most of the energy from a mobile phone is absorbed by the skin; therefore, the risk of skin cancer of the head was also investigated. No evidence of an increased risk was reported from a cohort subdividing the entire Danish population into subscribers of mobile phones between 1982 and 1995 and non-subscribers or later subscribers (Poulsen et al., 2013). In general, it appears that the more recent studies attenuate the findings of previous mainly case-control studies, but prospective studies enrolling specifically the heaviest users of mobile phones are merited.

### Other major activities on environmental and radiationrelated risk factors

To address the disproportionately high incidence rates of oesophageal squamous cell carcinoma in East Africa and Southern Africa, ENV established a research network from six countries across the region. Its kick-off meeting was held in September 2013 to decide on research priorities primarily focused on the evaluation and identification of setting-relevant modifiable environmental and lifestyle risk factors for this disease.

A pilot case–control study was conducted on lifestyle factors and upper digestive tract cancers in Addis Ababa, Ethiopia, in collaboration with national and United States partners. This first feasibility study completed in Africa is identifying requirements of a full-scale case–control study to investigate the role of suspected risk factors (e.g. khat chewing; Figure 9) and established risk factors (e.g. tobacco, alcohol) for cancers of the oral cavity, pharynx, and oesophagus. The study enrolled 410 cases and controls between May 2012 and April 2013, and data analyses are under way. Figure 8. Observed time trends in the incidence rate of glioma among men aged 40–59 years in the Nordic countries (Denmark, Finland, Norway, and Sweden) compared with predicted changes in the incidence rates if 10 years or more of regular mobile phone use were to be associated with an increase in glioma risk of 100%, 50%, or 20%, respectively. Figure compiled from data in Deltour *et al.* (2012). RR, relative risk.

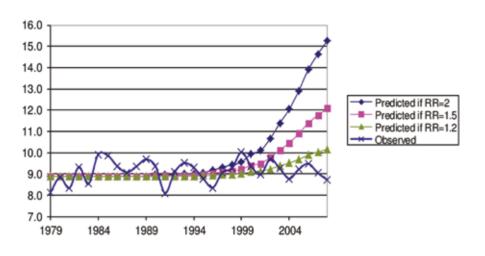


Figure 9. Khat, a plant chewed in Yemen and East Africa, contains amphetamine-like stimulants and is classified as a drug of abuse by WHO. However, its production and consumption is legal in several countries, including Ethiopia, where khat chewing remains popular at social gatherings, particularly among Muslim men. It is unclear whether khat chewing is associated with an excess risk of upper digestive tract cancer; additional research is needed to clarify this. © IARC/Joachim Schüz.



A retrospective cohort study is being conducted on cancer mortality in chrysotile asbestos miners and millers (Schüz et al., 2013). The world's largest open-pit chrysotile mine and its processing mills are located in Asbest, where approximately 20% of the world's chrysotile is currently produced (Figure 10). The overall aim of the study is to more precisely characterize and quantify the exposure-response relationship for total and site-specific cancer risks associated with exposure to chrysotile asbestos. The cohort is currently being enumerated and its expected size is approximately 30 000 workers.

Inter-individual variations in response to radiation after the Chernobyl nuclear accident suggest that genetic factors may also affect the risk of radiation-related papillary thyroid carcinoma (PTC). This was investigated by genotyping 83 cases and 324 matched controls sampled from children living near Chernobyl (Damiola et al., 2013). Associations with PTC were found for rs1801516 (D1853N) in ATM (odds ratio, 0.34) and rs1867277 in the promoter region of FOXE1 (odds ratio, 1.55). This suggests that both the DNA double-strand break repair pathway and the thyroid morphogenesis pathway are involved in the etiology of PTC, and that risk alleles and radiation dose act as independent multiplicative risk factors.

IARC has previously published data on cancer risk of workers in the nuclear industry. In an update, pooled follow-up data were analysed for nuclear workers from France, the United Kingdom, and the USA, which contained more refined adjustments for neutron doses compared with the previous studies. This will improve estimates of cancer risk related to radiation exposure within the workplace.

Cancer risk in adults after exposure to ionizing radiation in utero is currently being analysed in the cohorts of the exposed Southern Urals populations (SOLO project). The cohort consists of 11 000 persons exposed to radiation from releases of nuclear waste into the Techa River and 8000 persons born to workers of the Mayak nuclear facility, making it the largest data set worldwide to address this question. The highest doses were received by those born in the 1950s Figure 10. About 20% of the world's chrysotile used today is from mines in the town of Asbest, Russian Federation. A retrospective cohort study was initiated to investigate the chrysotile-related cancer risk in workers. © IARC/Joachim Schüz.



and mainly exposed through nuclear accidents, inappropriate waste dumping, and insufficient worker protection.

In April 2013, a feasibility study (SEMI-NUC) was initiated to assess the prospects of establishing a long-term, prospective cohort study of residents near the former Semipalatinsk nuclear test site (Figure 11). As study coordinator,

Figure 11. The Semipalatinsk nuclear test site. Photograph courtesy of the Institute of Radiation Safety and Ecology, Kazakhstan.



ENV hosted a kick-off meeting inviting partners and experts from Kazakhstan, Norway, Japan, the Russian Federation, and the USA to discuss issues related to this project.

The Global Acute Leukaemia network (GALnet), a newly established network of paediatric oncologists and epidemiologists from 18 countries around the world, will conduct collaborative studies to better estimate the worldwide burden of childhood leukaemia, identify causes of the disease, and create an information exchange network to discuss treatment options. GALnet is the result of a pilot project led by IARC with a kick-off meeting held in Lyon in February 2013.

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