

# Chemicals' Risks versus Radiation Risks with Respect to the Alteration of Human Sex Odds: A Preliminary Evaluation Approach

**Kristina Voigt<sup>1</sup>, Hagen Scherb<sup>1</sup>, Ralf Kusmierz<sup>2</sup>**

*Helmholtz Zentrum München – German Research Center for Environmental  
Health*

*Institute of Biomathematics and Biometry*

*Ingolstädter Landstr. 1*

*D-85764 Neuherberg, Germany*

*<sup>2</sup>Bremen*

e-mail: [kvoigt@helmholtz-muenchen.de](mailto:kvoigt@helmholtz-muenchen.de), [scherb@helmholtz-muenchen.de](mailto:scherb@helmholtz-muenchen.de),  
[ralf.kusmierz@bremen.de](mailto:ralf.kusmierz@bremen.de)

## **Abstract:**

The ratio of male to female offspring at birth may be a simple and non-invasive way to monitor the reproductive health of a population. Except in societies where selective abortion skews the sex ratio (SR), approximately 105 boys are born for every 100 girls. It is said that the sex ratio at birth is remarkably constant. In a systematic review, 100 studies were examined concerning possible environmental or occupational sex odds determinants, like e.g. ionizing radiation or chemicals.

In a recently published study by the authors the effect of ionizing radiation on the alteration of sex odds in the vicinity of German nuclear facilities was investigated. The authors revealed an increase in the sex odds. We now want to investigate whether chemical sites also influence the human sex odds at birth.

To assess spatial, temporal, as well as spatial-temporal trends in the sex odds and to investigate possible changes in the vicinity of chemical plants, we apply ordinary linear logistic regression.

The current study is considered a first screening approach applying the same methodology on chemical sites as in sex odds study in the vicinity of German nuclear facilities. In this approach 10 chemical sites in Germany (large chemical plants and chemical parks) were taken into consideration. It can be demonstrated that small alterations take place in the vicinity of large chemical plants. Furthermore, stronger changes in sex odds can be observed in the vicinity of the investigated chemical plant where an accident took place.

**Keywords:** *sex ratio; chemical plants in Germany; chemical parks in Germany; logistic regression.*

## **1 INTRODUCTION**

The concept of the exposome, representing the totality of exposures received by a person during life, encompasses all sources of toxicants, e.g. chemicals and radiation as well as stress, life-style etc., and, therefore, offers scientists an approach for investigating the environmental causes of chronic diseases [Rappaport, 2011].

Epidemiological effects of environmental pollution can be modelled in many different ways. An important indicator is the human sex ratio at birth. Sex ratio is the ratio of males to females in a population. In this iEMSs Conference 2012 three contributions are presented concerning this important indicator. One by Kusmierz et al. treating the data sources / statistical databases which are exploited, the

second one by Scherb et al. treating the changes in sex odds around nuclear facilities, and this paper concerning the differences in human sex odds around chemical plants/parks.

The ratio of male to female offspring at birth may be a simple and non-invasive way to monitor the reproductive health of a population. Except in societies where selective abortion skews the sex ratio (SR), approximately 105 boys are born for every 100 girls [Ein-Mor et al., 2010]. The authors concluded from a large retrospective cohort study that the sex ratio at birth is remarkably constant. In a systematic review of 100 studies, Terrell et al. [2011] examined whether environmental or occupational hazards alter the sex ratio at birth. The authors evaluated chemicals as well as radiation.

In a recently published study [Kusmierz et al., 2010], [Scherb and Voigt, 2011] the effect of ionizing radiation on the alteration of sex odds in the vicinity of German nuclear facilities was investigated.

As indicated by Terrell et al. [2011] some chemicals also showed an effect on the sex ratio in certain studies.

In the current paper we want to take a closer look at the sex odds around German chemical plants and find out if the sex odds is distorted by chemicals' production or not. To assess spatial, temporal, as well as spatial-temporal trends in the sex odds and to investigate possible changes in the vicinity of chemical plants, we will apply ordinary linear logistic regression.

Occasionally available datasets are large but interesting or relevant differences in sex odds are small. For example 100 000 cases are needed to achieve a significant result with a probability of 80% when testing the null sex odds 1.06 against 1.08, and approximately 400 000 cases are required for an 80% power if the 'true' alternative sex odds under exposure were only 1.07. Note that the statistical power is even more reduced in case of a two-sample problem where no reference is made to a 'true' null parameter, but two independent populations are compared instead. Even for 100 000 exposed and 100 000 non-exposed births the power would be only 54% to detect an increase from a normal sex odds of 1.06 to a disturbed sex odds of 1.08. Nevertheless, several hundreds of female concepts might be affected detrimentally in such a hypothetical situation under the conservative assumption that only the female gender was susceptible [Scherb and Voigt, 2009].

## **2 CHEMICALS CAN ALTER HUMAN SEX ODDS**

Altered human sex odds at birth may be indicative of general health detriment or genetic damage under unfavorable environmental conditions for parents before conception, embryogenesis, pregnant women, or the fetus [Moracelli et al., 2000], [James 2006], [Beratis et al., 2008], [James 2008, 2010], [Ruckstuhl et al., 2010]. A distinct, however unexplained, seasonality of the monthly sex odds was reported by Lerchl [1998]. Maternal exposure to PCBs may be detrimental to the success of male sperm or to the survival of male embryos. Findings could be due to contaminants contained in industrial PCB products, to metabolites of PCBs, or to PCBs themselves [Hertz-Picciotto et al., 2008]. Hence more girls were born. In a commentary entitled "Where the boys aren't: dioxin and the sex ratio", Clapp and Ozonoff [2000] summarized the results of several studies where the exposure to dioxins entailed an alteration of the sex odds towards fewer boys. Hence more girls were born. In a study performed in the state of Michigan in a well-defined period of PBB or PCB parental exposure, the odds of a male birth increased [Terrell et al., 2009]. Hence more boys were born. In a review article by Terrell et al. [2011] chemicals either induced an increase or decrease in the sex odds.

## **3 EVALUATION OF 10 CHEMICAL SITES IN GERMANY**

### **3.1 Selection of chemical sites to be evaluated**

The German chemical industry represents sales of 158 billion € and is the biggest producer of chemicals in Europe [VCI, 2011]. Many chemical sites are clustered in so-called chemical parks. These chemical parks provide the platform of success for the German chemical industry according to the Verband der Chemischen Industrie (VCI) in Germany [VCI, 2011].



Figure 1. Chemical Parks in Germany [VCI, 2011]

Approximately 60 chemical parks exist in Germany, many of them are found in the three German states Rhineland Palatinate, Hesse and Saxony-Anhalt (see Figure 1). A list of the chemical parks in Germany can be found under the URL: <http://www.chemicalparks.com/parks/Seiten/CompleteList.aspx>.

We selected 10 parks including the sites of the large German chemical industry locations Bayer, BASF, Hoechst and the former German Democratic Republic chemical companies, Leunawerke, Buna-Werke and the region Bitterfeld. This approach has to be understood as a first screening to find out whether the chemical industry sites have any influence on the sex odds.

Table 1. Selected Chemical Parks / Chemical Industry Sites in Germany

Company	Location	German state	GK3 Coordinates [km]	
			R	H
Bayer AG	Leverkusen	North-Rhine-Westphalia	3358,5	5655,1
BASF	Ludwigshafen	Rhineland-Palatinate	3459,0	5484,5
Hoechst	Frankfurt am Main	Hesse	3466,8	5550,4
Chemiepark, Chem. Werke Hüls	Marl	North-Rhine-Westphalia	3368,4	5729,4
Chemiepark Kalle Albert	Wiesbaden	Hesse	3446,3	5544,3

Industriepark Werk Gerndorf	Burgkirchen	Bavaria	3777,4	5344,7
Leunawerke	Leuna	Saxony-Anhalt	3709,8	5691,4
Chemiepark Bitterfeld-Wolfen	Bitterfeld-Wolfen	Saxony-Anhalt	3730,3	5726,4
Buna-Werke GmbH Schkopau	Schkopau	Saxony-Anhalt	3706,6	5698,5
BASF Schwarzheide	Schwarzheide	Brandenburg	3839,4	5716,6

In Table1 we list the 10 chosen chemical industry sites. The location as well as the German state and the GK3 coordinates are given.

### 3.2 German municipalities 1957 to 2010

Kusmierz et al. [2010] compiled official gender specific annual live births statistics for all municipalities in Germany. To calculate the distances of the municipalities from nuclear facilities, we determined uniform coordinates for the geographic positions of those municipalities including the geographic positions of 28 pertinent nuclear facilities including all nuclear power plants in Germany and Switzerland. We now use the same data background for the evaluation of the sex odds in the vicinity of chemical sites in Germany

### 3.3 Statistical Methods

To assess time trends in the occurrence of boys among all live births, and to investigate whether there have been significant changes in the trend functions in 1957 or later, we applied ordinary linear logistic regression. This involves considering the male proportion among all male (m) and female (f) births:  $p_m = m/(m+f)$ . Important and useful parameters in this context are the sex odds:  $SO = p_m/(1 - p_m) = m/f$ , and the sex odds ratio (SOR), which is the ratio of two interesting sex odds if those two sex odds have to be compared, e.g. in exposed versus non-exposed populations. We used dummy coding for single points in time and for time periods as well. For example, the dummy variable for the time window from 1994 on is defined as  $d_{94}(t) = 0$  for  $t < 1994$  and  $d_{94}(t) = 1$  for  $t \geq 1994$ . The simple and parsimonious logistic model for a trend and a jump in 1994 has the following form (LB = live births):

$$\text{Boys}_t \sim \text{Binomial}(\text{LB}_t, \pi_t)$$

$$\log \text{ odds } (\pi_t) = \text{intercept} + \alpha * t + \beta * d_{1994}(t)$$

To allow for changing sex odds trend slopes (broken sticks) after e.g. chemical accidents, we used dummy coding of time windows and interactions of those time windows with time. The data in this study were processed with Microsoft Excel 2003. For statistical analyses, we used R 2.11.1, MATHEMATICA 5.0, and mostly SAS 9.1 (SAS Institute Inc: SAS/STAT User's Guide, Version 9.1. Cary NC: SAS Institute Inc; 2003).

## 4 RESULTS OF THE LOGISTIC REGRESSION APPROACH ON 10 CHEMICAL SITES

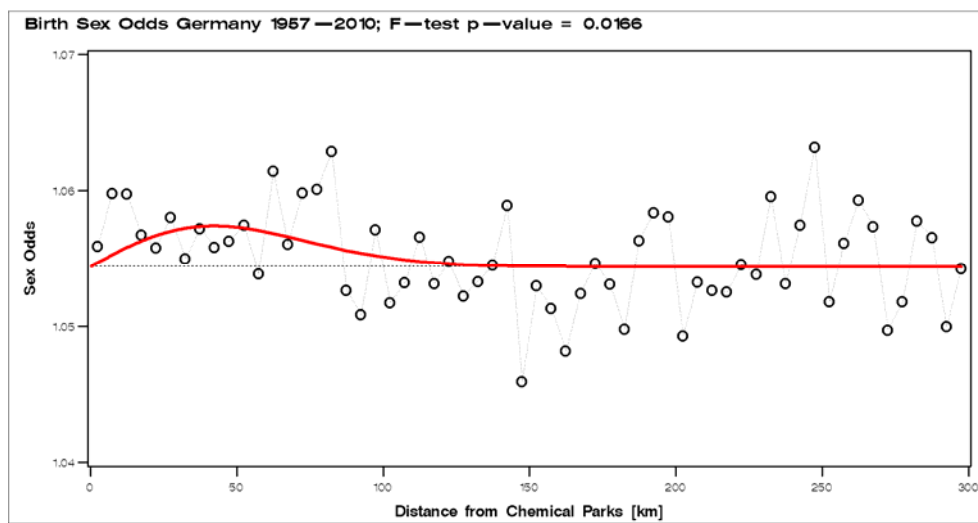
The data evaluation is carried out in two steps. In the first place we take a look at the complete data set of 10 chemical sites and want to find out whether the sites have an impact on the sex odds in the vicinity of the locations. In a further data evaluation step we put the focus on those companies which had a major chemical

accident within the time span of our geographical data that is to say between 1957 and 2010. The underlying data set comprises 33 million births.

#### 4.1 Logistic regression model applied on the chosen 10 chemical sites

A study performed by the authors [Kusmierz et al., 2010] and [Scherb and Voigt, 2011] revealed an increase in sex odds in the vicinity of running nuclear facilities. A further investigation revealed significant and strong increase in sex odds around the nuclear storage site TBL (Transportbehälterlager: nuclear waste shipping casks storage) Gorleben in Lower Saxony, Germany [Scherb and Voigt under review, 2012]. As outlined in section 2, several studies showed that chemicals may also alter the sex odds.

We therefore performed the same data analysis within the vicinity of 10 selected chemical sites. The result of this first screening approach is given in Figure 2. Note: The resolution on the ordinate is adjusted according to the variability of the data. (This also applies to Figure 3).

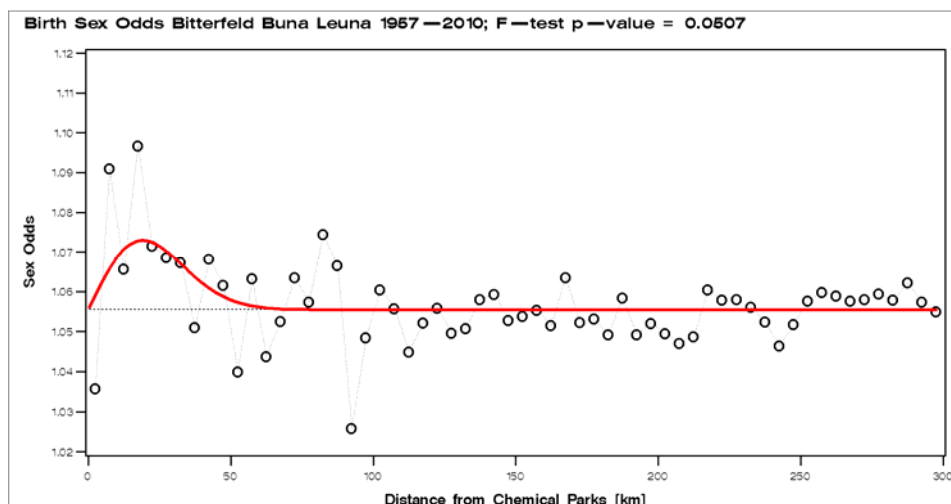


**Figure 2.** Sex odds around 10 selected Chemical Parks in Germany

We can detect a slight increase in the sex odds in a peak distance of 42 km from the sites. As the p-value (an indicator for the significance of the data analysis) is 0,0156, the overall inspection of all 10 sites shows a significant effect.

#### 4.2 Logistic regression model on the examples: Bitterfeld, Buna, Leuna

We calculated the sex odds around the 10 chosen chemical sites separately. We received noisy results with p-values from 6 % to 73 %. We therefore decided to take a look at the cluster of chemical sites in Bitterfeld, Buna and Leuna. The result is presented in Figure 3.



**Figure 3.** Sex odds around chemical sites in Bitterfeld, Buna and Leuna

As can be clearly noticed, there is a significant peak at the distance of 19 km. The p-value is 5 %, which indicates statistical significance.

#### 4.3 Influence of chemical accidents on the sex odds

Major industrial accidents provide examples where the exposure status of large populations may change considerably within relatively short time intervals of days or weeks (e.g. Seveso herbicide plant explosion, Chernobyl Nuclear Power Plant catastrophe). Scherb and Voigt [2009] investigated the human sex ratio at birth in several European countries before and after the Chernobyl Nuclear Power Plant accident. A long-term chronic impact of radioactive fallout on the secondary sex ratio, that is to say an increase in the human sex odds was found. We now set up the hypothesis that also major chemical accidents have an effect on the human sex odds. A central unit for collection and evaluating major accidents was established in 1993 at the German Umweltbundesamt [Uth and Wiese, 2004]. It can be found under <http://www.umweltbundesamt.de/nachhaltige-produktion-anlagensicherheit-e/zema/index.html>. Only annual reports are available on that WebPage and no direct search for accidents.

A major chemical accident occurred on 22 February 1993 at the plant Griesheim of Hoechst AG Frankfurt/Germany during which approximately 11.8 tons of chemical mixtures containing mostly chlorinated nitroarenes were emitted leading to serious contaminations in Schwanheim/Goldheim, a nearby housing area. Numerous inhabitants of the contaminated area complained of irritation of eyes, skin and mucous membranes, headache and nausea, and 92 persons with moderate symptoms were reported to the National Health Department [Heudorf et al., 1994].

We therefore took a closer look at the live birth sex odds in the vicinity of Hoechst – Griesheim (see Figure 4). Here we detected a remarkable decrease in sex odds after the chemical accident. The p-value 0,0276 indicates a considerable significant effect.

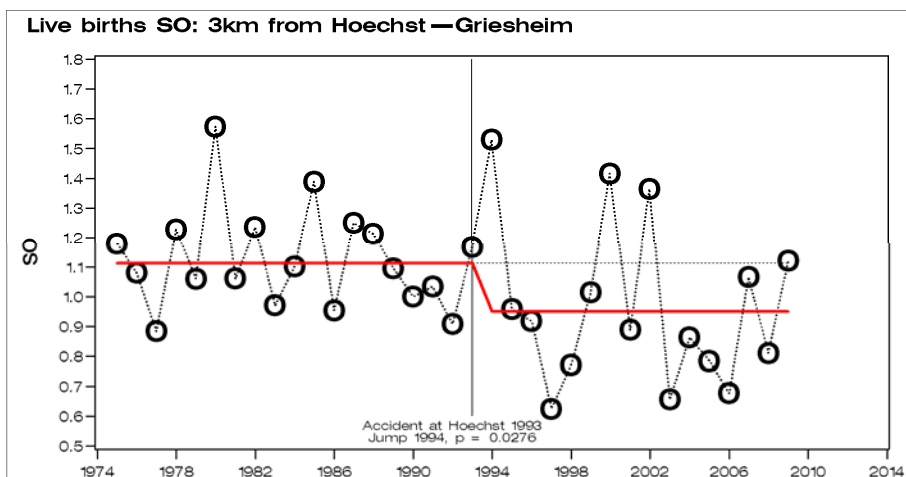


Figure 4. Sex odds 3 km from Hoechst-Griesheim

For this graphical output 5.203 live births were considered.

## 5 CONCLUSIONS AND RECOMMENDATIONS

Human sex ratio at birth, conventionally expressed by the number of male live births per 100 female live births, is about 105-106 and remarkably constant [Ein-Mor et al, 2011]. Some environmental hazards can alter the sex ratio at birth. In a recently published review article [Terrell et al, 2011] 100 studies were evaluated. Several studies concerning the impact of chlorinated organic compounds were looked upon. The review by Terrell et al. showed no consistent trend. Some studies indicated an increase whereas others a decrease. It has to be mentioned that only very few number of births (ranging from 17 to 6180) were taken into consideration in the studies reviewed. Studies on chlorinated chemicals like those of Weisskopf et al [2003] and of Rogan and Ragan [2007] revealed a decrease in the human sex odds at birth.

In our first screening approach where we took a look at 10 large chemical sites in Germany as an example, we found some indications that the sex odds might be affected by the running chemical sites. The study performed for the alteration of sex odds in the vicinity of German running nuclear facilities clearly indicated an increase in sex odds (see also Scherb et al. in this proceedings volume).

Furthermore, we made one investigation around a chemical plant where a major chemical accident took place in 1993. Here we found a significant effect on the sex odds, say a decrease in sex odds.

The studies on sex odds with respect to accidents with ionizing radiation clearly indicated strong effects in the direction of an increase in sex odds [Scherb and Voigt, 2009, 2011].

Both increase and decrease in the human sex odds at birth provide a strong indication that there is an impact of man-made facilities on the human genome. Further background concerning this issue is given by Sperling et al. [2012].

Further studies concerning the effect of chemical sites, chemical accidents should be performed to underlay and verify our findings presented in this paper.

## REFERENCES

- Beratis, N.G., A. Asimacopoulou, and Varvarigou, Association of secondary sex ratio with smoking and parity, *Fertility and Sterility*, 89 (3), 662-667, 2008.
- Clapp R, and D. Ozonoff, Where the boys aren't: dioxin and the sex ratio, *Lancet*, 355 (9218), 1838-1839, 2000.

- Ein-Mor, E, D. Mankuta, D. Hochner-Celnikier, A. Hurwitz, and R. Haimov-Kochman, Sex ratio is remarkably constant, *Fertil Steril*, 93 (6),1961-1965, 2010.
- Hertz-Picciotto, I, T.A. Jusko, E.J. Willman, R.J. Baker, J.A. Keller, S.W. Teplin, And M.J. Charles, A cohort study of in utero polychlorinated biphenyl (PCB) exposures in relation to secondary sex ratio, *Environmental Health*, 7, 1-8, 2008.
- Heudorf, U, H.G. Neumann, and M. Peters, Accident in the Hoechst AG company 22 February 1993. 2. Public health evaluation, *Gesundheitswesen*, 56 (7), 405-410, 1994.
- James, W.H., Offspring sex ratios at birth as markers of paternal endocrine disruption, *Environmental Research*, 100 (1), 77-85, 2006.
- James W.H., Evidence that mammalian sex ratios at birth are partially controlled by parental hormone levels around the time of conception, *Journal of Endocrinology*, 198 (1), 3-15, 2008.
- James, W.H., Inconstancy of human sex ratios at birth, *Fertility and Sterility*, 94 (3), E53-E53, 2010.
- Kusmierz, R., K. Voigt, and H. Scherb, Is the human sex odds at birth distorted in the vicinity of nuclear facilities (NF)? A preliminary geo-spatial-temporal approach, In: Greve K., and A.B. Cremers (eds), Integration of Environmental Information in Europe, Bonn, 2010, Shaker Verlag, Aachen, 616-626, 2010.
- Lerchl, A., Seasonality of sex ratio in Germany, *Hum Reprod*, 13 (5), 1401-1402, 1998.
- Mocarelli, P., P.M. Gerthoux, E. Ferrari, D.G. Patterson Jr., S. M. Kieszak, P. Turner, and L.L.Needham, Paternal concentrations of dioxin and sex ratio of offspring, *Lancet*, 355 (9218),1858-1863, 2000.
- Rappaport, S.M., Implications of the exposome for exposure science, *J Expo Sci Environ Epidemiol*, 21 (1), 5-9, 2011.
- Rogan, W.J., and N.B. Ragan, Some evidence of effects of environmental chemicals on the endocrine system in children, *Int J Hyg Environ Health*, 210 (5), 659-667, 2007.
- Ruckstuhl, K.E., G.P. Colijn, V. Amiot, and E. Vinish, Mother's occupation and sex ratio at birth, *BMC Public Health*, 10, 269, 2010.
- Scherb, H., and K. Voigt, Analytical ecological epidemiology: exposure-response relations in spatially stratified time series, *Environmetrics*, 20 (6), 596-606, 2009.
- Scherb, H., and K. Voigt, The human sex odds at birth after the atmospheric atomic bomb tests, after Chernobyl, and in the vicinity of nuclear facilities, *Environ Sci Pollut Res Int*, 18 (5), 697-707, 2011.
- Scherb, H. and K. Voigt, Response to W. Kramer: The human sex odds at birth after the atomic bomb tests, after Chernobyl, and in the vicinity of nuclear facilities, *Environ Sci Pollut Res*, 19, 1335-1340, 2012.
- Sperling, K, H. Neitzel, H. Scherb, Evidence for an increase in trisomy 21 (Down syndrome) in Europe after the Chernobyl reactor accident, *Genet Epidemiol*, 36, 48-55, 2012.
- Terrell, M.L., A.K. Berzen, C.M. Small, L.L. Cameron, J.J. Wirth, and M. Marcus, A cohort study of the association between secondary sex ratio and parental exposure to polybrominated biphenyl (PBB) and polychlorinated biphenyl (PCB), *Environmental Health*, 8, 1-8, 2009.
- Terrell, M.L., K.P. Hartnett, and M. Macrus, Can environmental or occupational hazards alter the sex ration at birth? A systematic review, *Emerging Health Threats Journal*, 4 (7109), 2011.
- Uth, H.J., and N. Wiese, Central collecting and evaluating of major accidents and near-miss-events in the Federal Republic of Germany - results, experiences, perspectives, *Journal of Hazardous Materials*, 111 (1-3), 139-145, 2004.
- Verband der Chemischen Industrie eV, Chemical Parks in Germany. VCI. <http://www.chemicalparks.com/PressReleases/Documents/Chemieparks>, Accessed 02.02.2012, 2011.
- Weisskopf, M.G., P. Knekt, E.J. O'Reilly, J. Lyytinen, A. Reunanen, F. Laden, L. Altshul, and A. Ascherio, Persistent organochlorine pesticides in serum and risk of Parkinson disease, *Neurology*, 74 (13), 1055-1061, 2010.