

Epidemiologic study on the skin lesions of workers exposed to N,N'-methylene-bis-(2-amino-1,3,4-thiadiazole) and of children in the neighborhood of the factory

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QIAN C, LU MY, WANG XS, ZHAO HR, DONG ZH, GU XQ. Epidemiologic study on the skin lesions of workers exposed to N,N'-methylene-bis-(2-amino-1,3,4-thiadiazole) and of children in the neighborhood of the factory. *Scand J Work Environ Health* 11 (1985): suppl 4, 55—59. The air in a factory producing N,N'-methylene-bis-(2-amino-1,3,4-thiadiazole) (MATDA) and water in a nearby river were often polluted by the intermediate and finished product. The levels of MATDA in the air, soil, and river water were 0.1—0.8 mg/m³, 6—2 650 mg/kg, and 0.5—2 mg/kg, respectively. Seventy-nine workers engaged in MATDA production were observed; 44 % of them suffered from contact dermatitis; and 72 % showed changes of pigment in the skin (versus 2 and 16 %, respectively, for the referents). All of the exposed workers had experienced dermatitis at some time. For 218 pupils of a primary school in the neighborhood of the factory, the incidence of hypopigmentation and pigmentation of the skin was 14 and 72 %, respectively, but in the reference group the corresponding incidence rates were 0 and 20 %. Pigment changes of workers' children increased with the duration of residence in the neighborhood of the factory. The results of the survey led to a change in the formulation of the product from a powder to an emulsion. Improved technology was also initiated which allowed most of the waste to be reused in the processing. After these control measures the dermatitis of the workers was greatly reduced.

Key terms: dermatitis, hypopigmentation, MATDA, pigmentation.

N,N'-methylene-bis-(2-amino-1,3,4-thiadiazole) (MATDA), an effective bactericide to control *Xanthomonas oryzae* of rice, is tetratogenic in experimental animals (2) and can cause dermatitis in humans exposed in its production and use (4, 6).

MATDA has been produced for nine years in the Jianhu Pesticide Factory, which was built in 1975 and moved to a new building (workplace) about 20 m north of the old in 1980. Raw materials for its synthesis include hydrazine hydrate, ammonium thiocyanate, sulfuric acid, acetone, formic acid, formaldehyde, and alkaline liquid. The main intermediate of the process is aminothiurea. Synthesis is followed by centrifugation, drying in the sun, pulverization, and packing. Wastes from the synthesis and centrifugation processes are discharged into a water trough. Rinse water, containing MATDA and its intermediates from the factory grounds and containers, is directly discharged into a river in the vicinity, and thereby soil and water are polluted.

This study concerns the occurrence of dermatitis among the production workers of this factory and the skin pigment changes of children living near the factory.

Methods

For the detection of MATDA in the environment, area air samples were taken from the new workshop during all steps of production except synthesis and also from the ambient air, soil, and river water in the vicinity of both the new and the old factory buildings. Six water samples from other sources with no potential MATDA pollution were assayed to verify the reliability of the analytical method. An improved colorimetric analysis of trace MATDA in the samples with dimethylformamide as the solvent was used in the assay (1).

In the investigation of dermatitis and other skin lesions of the workers, 79 subjects (30 men and 49 women, age range 18—55 years) were observed; they accounted for 84 % of the workers in the MATDA workshop. They were examined physically and asked about any past history of dermatitis. Eighty-two workers from a cement factory comprised the reference group.

For the investigation of skin pigment changes caused by MATDA in the environment, a total of 281 primary school pupils (among them 38 boarding pupils) and 32 children from a kindergarden in the neighborhood of the factory were observed. The reference group was comprised of 133 pupils in another primary school three miles (approximately 5 km) away and 74 children from another kindergarden in town. All skin disorders were diagnosed by the same dermatologist.

To help identify the source of the MATDA pollution, we examined the skin pigment changes of the

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Table 1. Average concentration (three samples/site) of N,N'-methylene-bis-(2-amino-1,3,4-thiadiazole) in the air of the workshop and in the ambient environment.

	Concentration (mg/m ³)
<i>Air of workshop</i>	
Centrifugation	
Inlet	0.32
Outlet	0.48
Pulverization	
Inlet	0.80
Outlet	0.32
Packing	0.1
<i>Ambient environment</i>	
New workplace	
Drying court	0.44
Front of clerical building	0.2
North highway	Not detected
Old workplace	
Drying court	0.20
Waste trough	0.18
Road between factory and the primary school	0.14

Table 2. Average concentration (three samples) of N,N'-methylene-bis-(2-amino-1,3,4-thiadiazole) in the soil of workplaces near the factory buildings.

	Concentration (mg/kg)
<i>New factory building</i>	
Front of building (distance 5 m)	2 650
East of drying court	45
South of drying court	80
Waste outlet of processing workshop	27.5
Front of clerical office	6
<i>Old factory building</i>	
From pier near school	9
Along river near drying court	54
Northeast of drying court	
Distance 10 m	29
Distance 30 m	14
Village south of drying court	24

Table 3. Average concentration (three samples) of N,N'-methylene-bis-(2-amino-1,3,4-thiadiazole) in river water near the factory.

	Concentration (mg/kg)
<i>New factory building</i>	
Rinse water from workshop	
12 June 1980	3.0
Waste outlet of the processing shop	
12 June 1980	2.0
8 July 1980 ^a	1.7
11 July 1980 ^a	0.67
Distance 50 m upstream	
12 June 1980	2.1
8 July 1980 ^a	0
11 July 1980 ^a	0
Downstream from the waste outlet of whole factory	
Distance 20 m	
12 June 1980	1.8
Distance 50 m	
12 June 1980	2.0
Distance 100 m	
12 June 1980	1.3
8 July 1980 ^a	0
Waste outlet from whole factory	
8 July 1980 ^a	1.4
11 July 1980 ^b	1.6
New village pier	
Number 1	
12 June 1980	1.3
8 July 1980 ^a	0
Number 2	
12 June 1980	0.7
8 July 1980 ^a	0
Factory canteen pier	
12 June 1980	1.1
8 July 1980 ^a	0
11 July 1980 ^b	0.03
<i>Old factory building</i>	
Waste outlet from whole factory	
12 June 1980	1.7
11 July 1980 ^b	4.1
Brook near drying court	
12 June 1980	2.0
11 July 1980 ^b	2.9
School pier	
12 June 1980	0.5
11 July 1980 ^b	1.5

^a Sampled when the workshop was not operating.

^b Sampled after a heavy rain.

offspring of the workers in the new community of the pesticide factory. Ninety-five subjects ranging in age from 40 d to 25 years were observed.

Results

MATDA in the air of the workshop and in the ambient environment

MATDA production was primarily a manual operation, except for the synthesis process. The product had to be placed in and taken out of containers as many as eight times from the centrifugation process to packing. Detectable MATDA was present in the air of all the work areas, the highest concentration occurring at the feed inlet of the pulverization process and the lowest having been measured in the packing

area. No MATDA was detected in the air of a highway about 100 m downwind from the factory, but in the air of the old workplace, which had been out of operation for a year, MATDA was still detected in the air when the weather was humid (table 1).

The soil in front of the new workshop was the most severely polluted. Soil south of the drying court had the second highest level of MATDA. Even the soil in front of the clerical building, about 100 m away from the workshop and soil sampled from the old workshop had detectable MATDA (table 2).

Both the partly finished and finished MATDA product were dusty and tended, due to improper control measures, to fly about and fall on the soil in the process of the drying, pulverization, and packing. Raining and rinsing disseminated MATDA dust to nearby brooks or rivers. The first batch of water sam-

ples had detectable MATDA, while control samples from tap water and a remote river in village number 1 showed no detectable MATDA. The second and third batch of samples, however, gave contrary results to the first, although the water was sampled at the same cross-section of the river. This difference was due to a change in the conditions during the samplings.

Samples from the waste outlet of the processing workshop and that of the whole factory had detectable MATDA (table 3). The river was heavily polluted, as the concentration of MATDA showed a gradient downstream and was even detected upstream. All the samples taken at piers were positive for MATDA. Samples of water taken from other sources away from the factory were negative.

Dermatitis and other skin lesions of the production workers

There were two types of skin lesions usually seen on the workers exposed to MATDA. Dermatitis lesions were seen on exposed areas such as the face, especially around nostrils, lips, the neck, and hands. Freckle-like pigmentation areas were seen on the face. The incidence rate was 44 % for dermatitis, 72 % for pigmentation, and 1 % for hypopigmentation among the MATDA-exposed workers. These rates were all statistically significantly higher than those of referents from a cement factory (2, 15, and 0 %, respectively) (table 4).

The incidence of dermatitis and pigmentation classified according to the type of work done by subgroups of the MATDA-exposed workers showed no signifi-

cant difference. Only one worker with hypopigmentation was in the centrifugation process.

Women had a significantly higher incidence rate of pigmentation (86 versus 50 %, $p < 0.001$).

Pigment changes of children from a primary school and kindergarden near the factory

The principal skin lesions of children from a primary school and a kindergarden near the factory were freckle-like pigmentation on the face (figure 1) and hypopigmentation. Compared with the reference groups, the exposed groups of children had a significantly higher incidence of skin lesions. Children in different grades of the primary school had similar incidence rates (table 5).



Figure 1. Freckle-like pigmentation caused by exposure to N,N'-methylene-bis-(2-amino-1,3,4-thiadiazole).

Table 4. Skin lesions of MATDA-exposed workers. (MATDA = N,N'-methylene-bis-(2-amino-1,3,4-thiadiazole).

Subjects	Number observed	Dermatitis		Pigmentation		Hypopigmentation	
		Number	%	Number	%	Number	%
Pesticide factory workers	79	32	44*	57	72*	1	1
Cement factory workers (referents)	82	2	2	13	15	—	0

* $p < 0.001$.

Table 5. Skin pigment changes of children living near the factory.

	Number of persons observed	Dermatitis		Pigmentation		Hypopigmentation	
		Number of cases	%	Number of cases	%	Number of cases	%
Pupils from the primary school near the factory	281	1	0	201	72	40	14
Pupils from a reference school	133	—	0	26	20	—	0
Children from the kindergarden near the factory	32	—	0	9	28	7	22
Children from a reference kindergarden	74	—	0	3	4	—	0

* $p < 0.001$, both pupils and kindergarden children.

Table 6. Skin lesions of pupils by residential area.

Residential area	Number of persons observed	Hypopigmentation		Pigmentation	
		Number of cases	%	Number of cases	%
East of the factory	48	4	8	33	69
South of the factory	109	24*	22	83	76
West of the factory	21	2	10	13	62
North of the factory	49	7	14	36	75
Center (school)	54	3	6	36	66
Total	281	40	14	201	72

* $p < 0.05$.**Table 7.** Prevalence of pigmentation of new pupils according to their original living areas.

Original living area	Number of persons observed	Pigmentation	
		Number of cases	%
Villages near the factory	28	11	39
Other places	32	—	0
Total	60	11	*18

Table 8. Pigmentation of workers' children by age of the children.

Age (years)	Number of persons observed	Pigmentation	
		Number of cases	%
≤ 5	21	2	10
6—10	32	12	38
11—15	27	18	67
16—20	10	6	60
≥ 21	5	3	60
Total	95	41	44

Table 9. Prevalence of pigmentation of workers' children by length of residence near the factory.

Years lived near factory	Number of persons observed	Pigmentation	
		Number of cases	%
Since birth	87	41	47
Less than a year	8	—	0
Total	95	41	43

Comparisons among pupils from different living areas revealed that those who lived south of the factory (close to the old factory) had a significantly higher incidence rate (22 %) of hypopigmentation (but not of pigmentation) than others (table 6).

Another survey of 60 new pupils indicated that pigmentation occurred only in children who lived in villages near the factory (table 7).

Pigment changes of children of workers who live in the new factory community

An investigation of skin pigment changes by family unit showed an increasing incidence rate for the workers' offspring over 10 years of age (table 8). The skin pigment changes of these children were not associated with the work categories of their parents. The occurrence of pigmentation correlated significantly with duration of residence near the factory however (table 9).

Discussion

Whether or not MATDA can be widely applied in agricultural use has evoked much controversy because it causes skin changes in humans and birth defects in experimental animals. This study focused only on the skin changes.

Severe dermatitis of the production workers was traced to direct exposure to MATDA. All work processes from centrifugation to packing were primarily manual due to out-dated technological processes and inadequate facilities at the factory. In addition, because of repeatedly being placed in and taken out of containers (as many as eight times prior to the finished product), MATDA dust had a strong tendency to fly into the air of the workshop, contact exposed skin of the production workers, and produce contact dermatitis. This finding was dramatically illustrated by the fact that almost all of the MATDA-exposed workers developed contact dermatitis at least once, while workers from a nearby workshop and residents living near the factory had no history of dermatitis, although detectable MATDA was present in the ambient environment.

There have been two severe dermatitis events reported as a result of drinking MATDA-polluted water (several hundreds of milligrams/liter) by accident (5 and unpublished data of the Jianha County Health and Antiepidemic Station). It can be assumed that MATDA can produce dermatitis both through direct contact and through ingestion. The mechanism of dermatitis has been proved to be the antagonistic effect of MATDA against nicotinic acid (3). This phenom-

enon has already been proved by the fact that dermatitis in workers can be prevented or treated with good results by the administration of nicotinic acid or nicotinamide.

The results of this study showed that drinking water moderately polluted with MATDA (several milligrams per liter) was significantly associated with skin pigmentation of children in the neighborhood of the factory, as illustrated by (i) the association between pigment changes of children from primary schools and kindergartens and living area and (ii) the lack of association between skin pigmentation of workers' offspring and their parents' type of work. The pathogenetic mechanism of skin pigment changes may also be related to a depletion of nicotinic acid in the body. The skin lesions (dermatitis, hyperpigmentation, and hypopigmentation) vary according to the degree and duration of exposure. In cases of acute and high doses dermatitis is predominant, while, in low-level long-term exposure, pigmentation changes are predominant.

Direct discharge of waste water was the main source of pollution to the ambient environment, as shown by a gradient distribution of MATDA from the waste outlet to nearby brooks or rivers by which the schools and villages are located. Pollution of soil, repeatedly washed by rain, around both the old and new factory buildings constituted another source of water pollution.

Considering the close correlation of dermatitis and pigmentation with exposure to MATDA and MATDA-polluted water, we asked the production managers to improve the technology of the factory. The introduction of a colloidal suspension of MATDA, sometime in 1982, prevented dust from flying into the workshop air. In addition, reuse of two-thirds of factory waste water simultaneously along with storage of the rest in a water trough has minimized pollution of the ambient environment. At present, under normal conditions, contact dermatitis of the workers has been brought under control.

An investigation committee, including representatives of government agencies related to pesticide production and safe use, inspected four similar MATDA production factories and, because of poor MATDA production management and its adverse effect on production workers, ordered three factories to stop producing MATDA dust. Although MATDA effectively controls rice leaf blight caused by *Xanthomonas oryzae* and, with improved technology, work conditions were improved, the factory in our investigation was requested to reduce its production until a final decision on the toxic effect of MATDA can be made. It will be determined if the MATDA-induced skin changes have been completely prevented at a follow-up examination of workers in 1984.

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