Grand Rounds: An Outbreak of Toxic Hepatitis among Industrial Waste Disposal Workers

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Case Presentation
From May to September 2001, two women and three men working in an industrial waste treatment plant in Ulsan, Korea, developed acute hepatitis.

To more efficiently treat a larger quantity of waste, in May 2000 the plant introduced a new process solidifying liquid wastes through thermochemical reaction evoked by unsalted lime, thereby evaporating volatiles. During this process, workers put 100–250 drums (200 L) of liquid wastes and 7–12 tons of unsalted lime into a vat of 10 m × 25 m × 1 m. The thermochemical reaction started within 20 min, after which the workers stirred the mixture a few times with an excavator (Figure 1).

The reaction continued for at least 12 hr, becoming more explosive over time; it generated high temperature and intermittent firing, and profusely spread malodorous vapors. The warehouse had wide entrances on both sides, and all the window glass on the external wall had been removed, allowing the volatiles to spread throughout the factory (Figure 1). From May until November 2001, this process was carried out > 10 times each month. On 18 September 2001, we sampled the waste oils and solvents from the unsalted lime process and analyzed them by gas chromatography–mass selective detector (HP 5973 Series, Hewlett Packard, Wellesley, MA, USA). Because the process had been discontinued after the hepatitis outbreaks, we simulated this process on a smaller scale in the same building, where this process had been conducted. Several chemicals, including dimethylformamide (DMF), dimethyleacetamide (DMAC), and pyridine, were detected in some of the samples collected from a walk-through before and after the simulated process (Table 1).

Clinical course of the cases. Case 1, a 51-year-old male, had been employed in the plant since 1986 and moved to the unsalted lime process with two other co-workers in July 2000. In April 2001, he had a single episode of chest pain. In early May, while he was hospitalized for the operation of sudden onset retinal detachment, his liver function was abnormal [aspartate aminotransferase (AST), 317 IU/L; alanine aminotransferase (ALT), 156 IU/L; alkaline phosphatase (ALP), 225 IU/L; total bilirubin, 2.2 mg/dL]. Ten days later his liver function was improved. He returned to work in the separator process in September, and then moved to the dry evaporative incinerator in October. However, his liver function worsened in November and peaked in December (AST, 482 IU/L; ALT, 507 IU/L). After stopping work, his liver function normalized.

Case 2 was a male, 35 years of age, who had started work in the evaporative concentration process in April 1994 with case 1. In late June 2001, he felt severely fatigued and began taking herbal medication 1 July to relieve the fatigue. However, his fatigue did not improve, and he developed insomnia, sweating, and jaundice 10 July. Case 2 was admitted to the hospital on 12 July after developing ascites with abnormal results of liver function (AST, 1,982 IU/L; ALT, 1,226 IU/L; ALP, 420 IU/L). He was discharged after remission of liver function on 30 August. After returning to work, he had a car accident and received injections of muscle relaxants and nonsteroidal anti-inflammatory drugs (NSAIDs) once a day for 8 days. He returned to work again on 24 September, but jaundice developed again on 1 October. On admission to the hospital at that time, his liver function worsened (AST, 737 IU/L; ALT, 432 IU/L; ALP, 541 IU/L; total bilirubin, 13.7 mg/dL). His condition worsened after admission, with severely increased liver enzymes and jaundice (AST, 193 IU/L; ALT, 159 IU/L; total bilirubin, 37.6 mg/dL). He died on 14 October 2001.
Case 3, a 41-year-old female, had been a repair and maintenance worker since 1993. In early July 2001, she felt severe fatigue and took two packs of herbal medicine given to her by case 2. On 14 July, her liver function test was normal. However, 1 week later her urine darkened and jaundice developed in her eyes. She was admitted to the hospital on 30 July with markedly increased liver enzymes (AST, 1,670 IU/L; ALT, 1,223 IU/L; ALP, 495 IU/L). Her condition improved steadily, and she was discharged on 19 September 2001. After returning to her job for 3 days, she felt so fatigued that she did not return to the workplace afterward.

Case 4 was a female, 53 years of age. She had been working in the sorting process since September 2000. She developed jaundice early in August 2001 and was admitted to the hospital on 24 August suffering from severe nausea. Her liver enzymes were markedly elevated (AST, 2,315 IU/L; ALT, 1,754 IU/L), bilirubin was elevated, and jaundice and mild ascites developed. After being moved to a university hospital, her condition improved gradually and liver function normalized on 12 December.

Case 5, a 26-year-old male, was employed in February 2001 and had been working in the dry evaporative incineration process. He was admitted to the hospital on 20 October 2001 due to jaundice and severely abnormal liver function results (AST, 1,336 IU/L; ALT, 1,368 IU/L; ALP, 198 IU/L). His condition improved, and he was discharged 8 November.

Table 2 summarizes the employment and exposure history and clinical characteristics of cases 1–5. Figure 2 presents the clinical course of the cases as shown by AST concentration.

Liver biopsy was performed on all but one case (case 2) in December 2001 (Figure 3). The pathologic findings showed diffuse spotty hepatocytic necrosis. The portal tracts were slightly enlarged, and inflammatory infiltration was present in all cases. Clumped Kupffer cells containing periodic acid-Schiff (PAS)-positive material were abundant, especially around the terminal hepatic venule (Figure 3A). These findings were compatible with the remission stage of acute hepatitis and also with toxic hepatitis. Wide periporal necrosis was also identified in cases 1 and 4 (Figure 3D), and necrosis was found in the central-to-portal or portal-to-portal region, with bridging necrosis in all cases (Figure 3C). In case 4, regenerative nodules were present, suggesting the development of cirrhosis. Cholestasis and fatty changes were also evident in cases 4 and 3, respectively.

Markers for hepatitis A (anti-HAV IgM) and B (HBsAg, HBeAg, anti-HBs, anti-HBc IgM) were negative in all cases. Anti-hepatitis C (anti-HCV) was positive in one case (case 1), but HCV was not detected on polymerase chain reaction (PCR).

This study was approved by the institutional review board of Dongguk University, Gyeongju Hospital. Written informed consent was received from all of the cases.

Discussion

Clinical evaluation. Seven episodes of hepatitis occurred in the five cases. Two of the patients suffered double episodes, the second of which occurred after the patient returned to work and received possible reexposure to the hepatotoxic agent(s). All of the episodes, except two, were very similar in their clinical course, with the duration of illness between 4 and 15 weeks (median, 7 weeks). The disease onset was highly concentrated within a narrow time period between May and August 2001.

The laboratory findings were quite similar for all of the episodes. The ratio of the relative increase of the measured values over the upper normal limit of ALT (40 IU/L) to that of ALP (120 IU/L) was > 5 in all cases, indicating that the hepatic injury was primarily hepatocellular rather than cholestatic. The hepatic lesions with bridging necrosis were also compatible with laboratory findings and clinical course. These characteristic values correspond with acute hepatocellular injury according to international criteria for diagnosis and classification (Danan and Benichou 1993).

None of the cases had hematologic, renal, or central nervous system symptoms or signs, but all of them had respiratory discomfort and dyspnea on exertion. None of the cases was positive for the immunologic indices such as antinuclear antibody or anti-smooth muscle antibody, and none had fever. Their clinical courses were acute hepatitis of less than 3-month duration.

Two episodes were exceptional. The first episode for case 1 was asymptomatic, and the liver enzyme level was not as elevated as the other five episodes. Also, the R value [(maximum ALT/upper limit of reference value of ALT for the illness) ÷ (maximum ALP/upper limit of reference value of ALP for the same period)] of 9.0 was lower than that of the five typical episodes (12.8–27.2). Case 2’s second episode was also different from the other typical episodes, with a lower R (7.1) and a relatively rapid increase in bilirubin concentration and hepatic failure. This episode more closely resembled fulminant hepatitis rather than typical acute hepatitis.

One of the most common causes of acute hepatic injury in Korea is viral hepatitis (Chun et al. 2002). In our cases, viral markers for HAV and HBV were all negative. HCV markers were positive in two cases. Case 1 was positive for anti-HCV, but viral RNA was negative by PCR. This absence of active viral RNA makes it unlikely that the acute hepatic injury was caused by HCV. In contrast, case 4

Table 1. Results of environmental monitoring in five locations and analysis of three bulk samples.

| Chemical          | EC (area %) | DI (ppm) | ULP 1 (area %) | ULP 2 (area %) | ULP 3 (area %) | B-ULP1 (area %) | B-ULP2 (area %) | A-ULP (area %) |
|-------------------|------------|----------|----------------|----------------|----------------|----------------|----------------|---------------|
| 2-Butoxyethanol   | 0.63       | —        | 11.79          | 1.77           | 10.00          | 1.77           | 10.00          | 6.17          |
| MDA               | 1.93       | 2.05     | 2.67           | 1.66           | 2.09           | 2.52           | 2.35           | 2.35          |
| Cyclohexanone     | 2.17       | 0.87     | 1.75           | 1.75           | 2.35           | 1.75           | 1.75           | 2.35          |
| DMF               | 3.60       | 1.77     | 1.93           | 1.93           | 26.07          | 1.93           | 26.07          | 26.07         |
| Tetrahydrofuran   | 6.00       | 6.85     | 7.49           | 2.65           | 7.33           | 6.11           | 2.65           | 3.73          |
| Toluene           | 0.015      | 0.041    | —              | 8.996          | —              | 9.127          | —              | 1.39          |
| Xylene            | 0.026      | 7.846    | 8.052          | 8.052          | —              | 8.052          | —              | —             |
| Trichloroethylene | 5.44       | —        | 4.58           | 5.48           | 30.33          | 28.37          | 30.33          | 30.33         |
| 1,4-Butanediol    | 1.71       | 2.54     | 1.05           | 1.05           | —              | 1.05           | —              | —             |
| Tetracaine        | —          | —        | —              | —              | —              | —              | —              | —             |

Abbreviations: DI, dry evaporative incinerator; EC, evaporative concentrator; GC, gas chromatography; MSD, mass selective detector; ULP, simulated unslaked lime process.
was positive in HCV-PCR but was negative for anti-HCV. Therefore, it is possible that HCV contributed to the development of acute hepatitis in this case. The prolonged course of case 4, compared with the other cases (15 weeks vs. 4–8 weeks), and the mild cirrhotic changes on pathology suggest the possibility of a mixed etiology for the illness of case 4.

When we applied the criteria for the diagnosis of drug-induced hepatic injury, our cases were compatible with toxic (or drug-induced) hepatic injury (Benichou 1990; Danan and Benichou 1993; Maria and Victorino 1997).

Severe destruction of liver cells with bridging necrosis was noted in all cases. However, in severe cases (cases 3 and 4), a wide area of necrosis was observed; this may indicate a change to subacute necrosis, which represents the possibility of transformation into chronic hepatitis. Actually, one case (case 4) already exhibited early cirrhotic change on pathology.

The role of herbal medication and hepatotoxic drugs in the development of acute hepatic injuries in two of the cases is of interest. Case 2 took herbal medications for 2 weeks and case 3 took only two doses. The label of the herbal medication indicated 28 components, at least one of which can be hepatotoxic (genistein, a phytoestrogen) (Hwang et al. 2001). However, the main reason case 2 took the herbal medication was for severe fatigue, which is related to the development of toxic hepatitis. In a case report of toxic hepatitis caused by this herb component, Hwang et al. (2001) described a cholestatic hepatitis that developed after the ingestion of a daily dose 10-fold higher than that of our case 4 for a period of 7 weeks. However, the strong similarity of the pattern of increase in the liver enzyme concentration and the R value, the similar clinical course of cases 2 and 3, and the short-term use of the herbal medication strongly suggests that the herbal medication was not a significant factor in the development of toxic hepatitis in these two cases.

Furthermore, contrary to cases 2 and 3, most reported cases of hepatitis related to herbal medications have been cholestatic hepatitis (Breen et al. 1986; Chitturi and Farrell 2000; Hwang et al. 2001; Langmead and Rampton 2001; Larrey and Pageaux 1995). These authors elucidated that the role of the herbal medication could be minor or, at best, an aggravating agent, rather than being a causative agent. In the case of case 3, she had only two doses of the herbal medication after her clinical manifestation had begun.

The NSAIDs taken by case 2 are also a potential candidate as the cause of his hepatitis. He received one ampule of 100 mg tolperisone HCl (a muscle relaxant) and diclofenac-β-dimethylaminooethanol (diclofenac) 90 mg/day for 8 days. Tolperisone has been reported to be a potential causative agent for hepatitis (Breen et al. 1986; Chitturi and Farrell 2000; Hwang et al. 2001). However, the main reason case 2 took the herbal medication was for severe fatigue, which is related to the development of toxic hepatitis. In a case report of toxic hepatitis caused by this herb component, Hwang et al. (2001) described a cholestatic hepatitis that developed after the ingestion of a daily dose 10-fold higher than that of our case 4 for a period of 7 weeks. However, the strong similarity of the pattern of increase in the liver enzyme concentration and the R value, the similar clinical course of cases 2 and 3, and the short-term use of the herbal medication strongly suggests that the herbal medication was not a significant factor in the development of toxic hepatitis in these two cases.

Table 2. Clinical characteristics of the toxic hepatitis cases.

| Characteristic | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 |
|---------------|--------|--------|--------|--------|--------|
| Age/sex       | 51 years/male | 35 years/male | 41 years/female | 53 years/female | 26 years/male |
| Department    | Selection | Evaporator | Welding and cleaning | Welding and cleaning | Sorting waste |
| Job title     | Sorting and treating waste liquids | Controlling evaporator | Welding and cleaning | Welding and cleaning | Controlling incinerator |
| Employment dates | 20 December 1986–10 January 2001 | 18 April 1994 | 1 May 1993 | 1 May 1993 | 1 October 2000 |
| Onset         | April 2001 | Late June 2001 | Early July 2001 | Early August 2001 | Middle of 2001 |
| Date of admission | 1 May 2001 | 12 July 2001 | 30 July 2001 | 24 August 2001 | 19 September 2001 |
| Duration of illness (weeks)a | 2 (4) | 7 (9) | 8 (10) | 15 | 7 |
| Viral hepatitis markers | HAV, HBV marker (–) | HAV, HBV marker (–) | HAV, HBV marker (–) | HAV, HBV marker (–) | HAV, HBV marker (–) |
| Biopsy        | Hepatic damage | Bridging necrosis | Fatty degeneration | Cirrhotic nodule | Cholestasis |
| Comments      | 9.0/12.8b | 27.2/1.1b | 23.1 | 24.5 | 19.7 |

Abbreviations: +, positive; –, negative.

*aTime period between admission and the remission of the AST and ALT. b1st illness (2nd illness). c(Maximum ALT/upper limit of reference value of ALT for the illness) d(maximum ALP/upper limit of reference value of ALP for the same period).
hepatotoxic in animals but not in humans. In this case, the dosage given was much smaller than the reported toxic dosage. However, we could not completely exclude the possibility that it might have exaggerated his hepatitis during his second return to work.

Diclofenac has been reported to be a hepatotoxic compound (Bhogaraju et al. 1999; Breen et al. 1986; Helfgott et al. 1990; Iveson et al. 1990; Ouellette et al. 1991; Purcell et al. 1991; Ramakrishna and Viswanath 1994; Scully et al. 1995). From an evaluation of 180 cases of diclofenac hepatotoxicity, Banks et al. (1995) reported that the hepatotoxicity was usually asymptomatic, with a few mild symptoms. About 1–5 cases of diclofenac hepatotoxicity developed per 100,000 prescriptions, with the average latency of 3–12 weeks.

**Epidemiologic evaluation.** Forty-eight workers (36 blue-collar workers and 12 office workers or drivers) have been working in this plant since 2001, and 6 workers, including two cases, retired after this outbreak of hepatitis. We evaluated liver function tests, ultrasonography, and immunologic markers of viral hepatitis in all employees except the three cases admitted to the hospital and three other absences. Two of them had mildly increased liver enzymes, and both had a previous history of abnormal liver function tests. One was suspected of having alcoholic liver disease and the other suffered from fatty liver due to being overweight. Based on ultrasonography, we suspected that 6 workers had fatty liver, which is one of the most common liver disorders among Korean workers (Cheong and Kim 1997). Another worker was suspected of having chronic hepatitis on the basis of ultrasonography, but did not have an abnormal liver function test. Of the 6 retired workers, 2 had chronic liver disease. A review of medical records showed that both had elevated liver enzyme levels from early 2001, both had positive HBV markers, and one was diagnosed with liver cirrhosis related to HBV and alcoholic liver disease. Therefore, they were not included in the cases. The incidence of toxic hepatitis was 10.4% in all of the workers and 13.9% in the production workers.

All of the cases developed within a 4-month period, from May to September 2001. Four of them occurred in a 2-month period, between mid-July and mid-September 2001. Even the recurrent cases of hepatitis occurred in this period. This phenomenon of heavy clustering over a narrow time span strongly suggests a possible association with exposure to toxic agents. The duration of illness in these cases was 4–15 weeks (median, 7 weeks).

All cases were production workers who had either participated in the unslaked lime process or worked nearby. In contrast, none of the workers who worked far from the unslaked lime process (e.g., laboratory, office, and waste water treatment staff) had hepatitis (Figure 4).

**Inference on the etiology.** We suspect that the unslaked lime process is responsible for the development of this toxic hepatitis outbreak for the following reasons: (a) during the 2 years before the outbreak, there were no significant changes in the amount and composition of the wastes or in the origin of the raw waste materials, except for the introduction of this unslaked lime process; (b) no cases of hepatitis occurred before the introduction of the unslaked lime process; and (c) simulation of the unslaked lime process showed that several

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**Figure 2.** Clinical course for each case shown by AST level. Seven episodes of acute hepatic injury occurred in five workers from the plant. Case 1’s first episode occurred in May 2001, but the episode was limited only to laboratory findings. Most of the clinical episodes of acute hepatic injury occurred between July and September 2001. The second episodes of cases 1 and 2 developed after they returned to work.

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**Figure 3.** Pathologic findings of toxic hepatitis cases. (A) PAS-stained liver from case 5 showing spotty necrosis of hepatocytes and clumped Kupffer cells containing PAS-positive material (arrows); these findings are compatible with the remission stage of acute hepatitis and with toxic hepatitis (magnification, 400×). (B) Hematoxylin and eosin (H&E)–stained liver from case 1 showing portal tracts that are slightly enlarged and infiltrated with inflammatory cells (magnification, 400×). (C) H&E-stained liver from case 5 showing central to portal bridging necrosis (magnification, 200×). (D) Masson trichrome staining of liver from case 4 showing wide perportal necrosis extending into the portal-to-portal area, with regenerative nodules present (magnification, 100×).
hepatotoxic materials are generated in the waste and vapors. Investigations on the other possible sources, including drinking water, food supply, and specific process in each warehouse, did not suggest any other causative factors. The phenomenon of the highly time- and place-dependent clustering of the cases can be explained by the predominant wind direction. Annual climate data shows that the wind direction in July was from the southwest toward the northeast, the direction from the vapor source toward the victims; this explains the clustering of the cases between July and September.

Considering the clinical, epidemiologic, and pathologic characteristics, the derivable clues for causative agents of this outbreak are as follows: (a) the main exposure occurred between June and August 2001; (b) the agent should cause acute necrosis of liver parenchyma; (c) an endogenous toxin is more relevant than an idiosyncratic reaction for the hepatotoxicity in these cases, given the relatively high incidence, although there is still a possibility of idiosyncrasy in view of the fact that cases 1 and 2 had eosinophilia and experienced a more severe, even fatal, relapse after reexposure; (d) the zonal type of necrosis of hepatocytes was present, mainly zone I (peribortal), but zone III (central vein) was also present in some of the cases; (e) steatosis and cholestasis were only occasionally observed; (f) the exposure route was suspected to be respiratory inhalation (neither oral intake nor skin absorption is plausible, considering the work processes and the raw material treated); (g) the agent is probably a highly potent hepatotoxin with sufficiently high vapor pressure and toxic potency, which by inhalation, can cause toxic hepatitis in workers at least 100 m away from the source; (h) the toxic activity of the agent should be specific to the liver without seriously affecting other organs or systemic effect; and (i) the agent appears to have a relatively long latency (> 2 weeks), and repetitive or chronic exposure could also accelerate the toxic reaction.

Taking into account these inferences, we tried to match the clinical, pathological, and toxicologic clues to the well-known hepatotoxic chemicals and those chemicals found in the samples from this industrial waste plant, such as DMF, DMAc, pyridine, and methyleneedianiline (MDA) (Bastian 1984; Hall 1992; Kopelman 1966; McGill and Motto 1974; Tillmann et al. 1997; Williams et al. 1974). For each toxicant, we listed the toxic properties and its clinical characteristics, but none of them completely matched the criteria for the potential causative agent in the current cases.

DMAC and DMAc, both solvents that can potentially cause acute toxic hepatitis (Baum and Suruda 1997; Choi et al. 2001; Kang et al. 1991; Kim et al. 1991; Marino et al. 1994; Spies et al. 1995), were detected in the environmental samples; such common solvents, which are used by many of the client industries of this plant, are likely to be the causative agents of this outbreak. Carbon tetrachloride is one of the strongest chemicals that can induce toxic hepatitis while showing hepatocellular necrosis with fatty change, but the clinical and pathologic characteristics we found do not correspond exactly with this agent, and it was not detected in our environmental samples. Pyridine, a hepatotoxin with its own peculiar odor, was also detected in the raw material samples (Baxter 1947; Carlson 1996; International Labor Office 1983; Pollock et al. 1943). Most of the hepatitis cases said that the vapor from the process was highly irritating; therefore, pyridine in the waste treated is a strong candidate. However, the environmental sampling was focused on the qualitative detection of the compound. Because the simulation of unslaked lime was performed on a much smaller scale than the true case and because the simulation was undertaken in November, the chemical composition may have varied significantly from that of June or August.

Another possibility is that the various chemicals detected in the analysis underwent an interaction among themselves, which synergistically raised their toxicity compared with the original material. Our cases showed relatively longer latency than usual toxic hepatitis; however, following the usual course of toxic hepatitis, there were no systemic symptoms or signs. Complex wastes have been evaluated for their toxicity (Meyer 1983; Simmons et al. 1988, 1994). It has been reported that the lowest dose of toxicity in a complex of several chemicals can be lower than that of any single chemical component, and latency can be longer (Dosing and Ranek 1984; Hodgson et al. 1989; Kimbrough 1983; Landrigan 1983; Neal 1983; Thilly et al. 1983). Simmons et al. (1988) suspected that toxic hepatitis could be caused by the synergistic interaction of various unknown chemicals generated during the unslaked lime process through thermochemical reactions.

In cases 2 and 3, herbal medicine and NSAIDs should be considered an aggravating factor—by synergistic or additive effect—on the liver damaged by hepatotoxic chemicals. However, we do not think they are the initiators. Cases 2 and 3 took the herbal medicine only after the severe fatigue had begun. Case 3 had only one dose of the herbal medicine after the symptom began. NSAIDs were given to case 2 after the recovery from the acute hepatic episode. Intravenous injection of NSAIDs, together with resumed exposure could have triggered fulminant hepatitis.

Conclusion

We conclude that this outbreak of toxic hepatitis developed as a result of exposure to the hepatotoxic materials generated during the treatment of industrial waste using unslaked lime. Between May and September 2001, five hepatitis cases occurred, including one death, due to fulminant hepatitis. The pathologic and epidemiologic findings clearly suggest that these cases of acute hepatitis were toxic hepatitis caused by occupational exposure rather

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**Figure 4.** Diagram of the industrial waste plant showing the work areas of the hepatitis cases. Case 1 worked in unslaked lime processing. Workplaces of the other cases were northeast from the unslaked lime process warehouse. In this area, the seasonal wind from the southwest is limited to July.
than viral infection or medication, such as herbal medicine and NSAIDs. In environmental samples, we detected several hepatotoxic chemicals, including pyridine, DMF, DMAc, and MDA, in addition to solvents such as toluene, styrene, and xylene. Although we could not confirm the exact causative agent among them, the latency of the illness and other clinical characteristics strongly suggests that one of the chemicals, or the synergistic effect of the interaction among the complex components, evoked the hepatitis.

In general, the processes of treating industrial waste are conducted in confined areas. However, this plant had invented a new adaptation to improve the original unsanitary process by introducing a thermochemical reaction. Waste oil or solvents are composed of many chemicals, with not only significant hepatotoxicity but also other organ toxicity. Therefore, these processes in the waste-treatment industry must be supervised and regulated under the direction of the public environmental protection authorities. Any arbitrary modification of such processes should be prohibited until the safety has been evaluated for any potential hazards to the environment and the workers.

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